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Pharmacy Compounding Advisory Committee

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CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
(703) 352-0091

PARTICIPANTS:

Members:
Randy P. Juhl, Ph.D., Chair
Igor Cerny, Pharm.D.
Judith Martin Riffee, R.Ph.
William J. Rodriguez, M.D., Ph.D.
Tony Welder, R.Ph.
Loyd V. Allen, Jr.,, Ph.D.
Carmen A. Catizone, M.S., R.Ph.
Elizabeth I. McBurney, M.D.
Sarah L. Sellers, Pharm.D.
Garnet E. Peck, Ph.D.
Christopher T. Rhodes, Ph.D.
William J. Rusho, R.Ph.
Lawrence Trissel, F.A.S.H.P.

Consumer Representative:
Rose-Ellen M. Hope R.Ph.

Industry Representative (non-voting):
David Liebman, R.Ph.

Industry Representative (non-voting):
Joan M. LaFollette, R.Ph.

Consultants to the Committee (Voting):
Kenneth B. Giddes, B.A., M.B.A. (Patient Representative)
(Voting on hydrazine only)

Guest Experts of the Committee (Non-voting):
Sid Gilman, M.D.
Janice Dutcher, M.D.

Guest Speakers:
E. William Rosenberg, M.D.
Christopher T. Bever, Jr., M.D.
Donald Sanders, M.D.
Andrew R. Blight, Ph.D.
Ronald Cohen, M.D.
Sharon Hamm, Pharm.D.
Dr. David Jacobus

TABLE OF CONTENTS

TABLE OF CONTENTS

P R O C E E D I N G S [8:30 a.m.]

Agenda Item: Call to Order/General Introductory Remarks

DR. JUHL: Good morning. Welcome to the second meeting of the Pharmacy Compounding Advisory Committee. We have a full couple of days worth of work to do. I think we will -- we have started on time and we will make every effort to end on time as well.

Our first order of business, if we could go around the table and have everyone introduce themselves and their position. We have members of the committee. We have FDA staff as well. And to remind you that you need to be relatively close to the microphone and speak to it and our transcriptionist will wave her hands if we are not doing a good job of speaking into the microphone.

So, let me start -- Dave, if you would begin for us, please.

DR. LIEBMAN: Good morning. I am David Liebman. I am a compounding community pharmacist.

MS. RIFFEE: Good morning. I am Judy Riffee. I am on faculty at the College of Nursing, University of Florida.

MS. LA FOLLETTE: I am Joan LaFollette. I work with Bristol-Myers Squibb in Princeton, New Jersey.

DR. SELLERS: Sarah Sellers, now from North Carolina, currently studying for the boards.

MR. CATIZONE: Carmen Catizone, representing the National Association Boards of Pharmacy.

MS. HOPE: Rose-Ellen Hope, consumer rep, associated with Public Citizen.

DR. JUHL: Rose-Ellen is a new member of the committee. Welcome.

MR. RUSHO: William Rusho, University of Utah.

MR. TRISSEL: Lawrence Trissel, University of Texas, M.D. Anderson Cancer Center.

DR. JUHL: Randy Juhl, University of Pittsburgh, School of Pharmacy.

DR. MC BURNEY: Elizabeth McBurney, dermatologist in private practice and on the clinical faculty at LSU Medical School in New Orleans.

DR. PECK: Garnet Peck, professor of industrial pharmacy, Purdue University.

DR. RODRIGUEZ: Bill Rodriguez, Children's Hospital and George Washington University.

DR. ALLEN: Loyd Allen, International Journal of Pharmaceutical Compounding.

MS. AXELRAD: Jane Axelrad. I am the associate director for Policy in the Center For Drug Evaluation and Research and one of the co-chairs of the Pharmacy Compounding Steering Committee that was created by FDA to address the FDA Modernization Act implementation.

I am going to introduce Lana, who isn't here yet, but my co-chair, Lana Ogram, who is the director of the Division of Prescription Drug, Compliance and Surveillance in the Office of Compliance in the Center for Drugs, will be joining us, I hope, shortly.

DR. DeLAP: Bob DeLap, FDA Office of Drug Evaluation 5. Our office includes the dermatology area.

DR. OKUN: I am Marty Okun. I am a medical reviewer, Division of Dermatologic and Dental Drug Products.

DR. JUHL: Thank you.

Our next order of business is the reading of the conflict of interest waiver by our executive secretary, Igor Cerny, who is taking care of details somewhere.

Jane Peterson, who will actually be our executive secretary for our next meeting.

Agenda Item: Conflict of Interest

MS. PETERSON: The following announcement addresses the issue of conflict of interest with regard to this meeting and it is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and research, which have been reported by the participants present pose no potential for an appearance of

conflict of interest at this meeting, with the following exceptions.

Since the issues to be addressed by the committee at this meeting will not have an impact on any particular compound, but rather may have widespread implications with respect to this industry, in accordance with 18 USC 208, the participants have been granted a waiver, which permits them to participate in today's discussion. Copies of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In the event that the discussions involve any other compounds or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose compounds they may wish to comment upon.

DR. JUHL: Thank you.

Well, at our first meeting in October to just review a little bit, we began the process of developing the bulk list of drugs that will be available for pharmacists to compound with. There were, I guess, two things that we did there,

not only review some individual drugs, but to begin to feel comfortable with the criteria of doing the same.

There were a number of drugs that we had on the list to consider last October that we were uncomfortable with making decisions on for reasons of their complexity or the lack of information. That leads us to our task today. We did the easy ones then. These are more difficult.

So, during our sessions for the next two days we will consider a variety of compounds for a variety of different maladies with a variety of different safety issues.

To kind of start us off, I would like to have Jane Axelrad make her introductory remarks.

Agenda Item: Introductory Remarks

MS. AXELRAD: First, I would also like to welcome everybody here. It was very difficult I understand for several of you to get here today and we really appreciate, you know, the effort that you made to get here. I would also like to introduce before I get into my remarks the other FDA staff who are in the room, some of whom we may be calling upon to answer questions. So, I would ask them to go around and introduce themselves.

DR. JUHL: Except we will need a microphone for them to do that.

DR. BROWN: My name is Paul Brown. I am a pharmacologist from the Division of Dermatologic and Dental

Drug Products in CDER.

DR. VIDRA: I am Jim Vidra, the review chemist for DNCB. I am also in the Derm and Dental Division.

DR. HATHAWAY: I am Dr. Steve Hathaway, a chemist with Derm and Dental.

DR. DeCAMP: Dr. Wilson DeCamp(?), chemistry team leader, Derm and Dental.

DR. COSMOS: Mary Jean Cosmos(?), supervisory project manager, Division of Dermatologic and Dental Drug Products.

DR. JACOBS: Abby Jacobs, pharm tox team leader, Derm and Dental Drug Products.

DR. O'CONNELL: Kathryn O'Connell, medical officer, Dermatologic and Dental Drug Products. I am filling in for Dr. Wilkin(?), who is the division director and he is out of town.

DR. TENNELLI: Good morning. Bob Tennelli, CDER, Office of Compliance.

DR. CHAMBERS: Wiley Chambers, deputy director, Division of Anti-Inflammatory Analgesic and Ophthalmic Drug Products.

DR. RICHMOND: Fred Richmond, team leader, Adverse Drug Reaction and Compounding Team within the Office of the Compliance.

DR. MITCHELL: Wayne Mitchell, Regulatory Policy

Staff here in CDER.

DR. BROWN: Ron Brown, pharmacist in the Office of Compliance.

DR. SCOTT: George Scott, pharmacist, Office of Compliance.

DR. HEINER: Betty Heiner(?), Federal/State Relations, Office of Regulatory Affairs.

DR. BASAT: Martha Gottem(?) Basat. I am chemist in the Dental Derm Division.

DR. JONES: Mike Jones, pharmacist, Office of the Center Director.

DR. LANDISH: John Landish, Office of Planning and Evaluation.

MS. AXELRAD: Thank you. I really wanted them to introduce themselves. Many of them are members of the Pharmacy Compounding Steering Committee and others are from the division that you will be hearing from this morning, who were involved in the reviews. Over the course of the next two days, you will be hearing from many other Center staff, who have been involved in reviewing these individual compounds because we have had the review divisions involved this time to a fairly extensive amount and they have done a lot of work, but they will introduce themselves as they come.

But I really wanted to recognize the people who have been contributing to our implementation effort. I also

want to thank the committee sort of more broadly for being willing to serve on this advisory committee. I know that it is really a lot of work for you all to prepare for the meetings and to come, but it is really very helpful for us to have a panel of distinguished experts to consult with as we work on implementing the law.

I am looking forward to productive discussions over the next two days.

It has been six months -- sorry -- seven months since we last met and we have been very busy during this interim period, working to implement Section 503(a) of the Food, Drug and Cosmetic Act, which was added by Section 127 of the FDA Modernization Act.

I would like to spend a few minutes bringing you up to date on our efforts over the past months and then we will begin our presentations on the drug substances that were nominated for the bulks list.

On January 7th of this year, we published the proposed rules in the Federal Register that would include a list of bulks drug substances that may be used in pharmacy compounding under the exemptions in Section 503(a) of the Act, even though they are neither the subject of a USP or NS monograph nor a component of an FDA-approved drug.

In that Federal Register notice and proposed rule, we proposed 20 drug substances for inclusion on the list,

based upon the recommendations we received from the committee at the October meeting. We indicated in the notice that ten additional substances were still under review by the Agency and we solicited comments on these substances. These are the substances that will be discussed with the committee today and tomorrow.

The proposed rule also included and requested comments on the criteria that the agency is proposing to use to determine whether a nominated substance should appear on the bulk drugs list. We discussed these criteria with the committee in October and the criteria proposed for comment reflected the deliberations of the committee.

The comment period for the proposed rule ended on March 23rd, 1999. The proposal generated over 190 comments from individuals or organizations. The vast majority of these comments, about 86 percent, were submitted by multiple sclerosis patients, friends of multiple sclerosis patients, physicians and other individuals in support of the drug substance 4-AP.

These comments were letter or e-mail testimonials about the benefits of 4-AP. Unfortunately, the comments did not include as much scientific or technical data about the use, safety or efficacy of 4-AP as we had hoped. But you will be hearing quite a bit about that this afternoon from our Review Division and a number of outside speakers.

The remaining comments on the proposed rule addressed a wider variety of issues. For example, several expressed support for one or more of the bulk drugs under consideration, especially the dermatological drug products, like chemtheradine(?), DNCB and squaric acid. Several expressed opposition to drugs under consideration, such as mild silver protein or poracetan(?) and several raised larger policy concerns about the Agency's overall efforts in this area.

We are in the process of evaluating these comments and preparing the final rule. The discussions today and tomorrow of the nominations of the substances to be included on the bulk drugs list that may be used in compounding will be considered when we develop the final rule. And, of course, this rule will never be actually final because it may continue to evolve as substances are added or removed from the list.

When the committee last met, we discussed 60 drugs that were being considered for inclusion on a list of drugs that have been withdrawn from the market, because they have been found to be unsafe or ineffective. When we discussed that list, we were concentrating on drugs that have been withdrawn from the market for safety reasons.

As you know, Section 503(a) provides the drug products that appear on a list of drug products published by FDA in the Federal Register, that have been withdrawn or

removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective may not be compounded under the exemptions in Section 503(a).

A proposed rule containing this list was published for comment before our last meeting on October 8th, 1998, and a final rule containing a list was published on March 8th, 1999. The committee has been provided copies of the final rule in background packages. And I believe there are copies available elsewhere.

The only comments concerning specific substances that we received on that rule were comments recommending against inclusion of adrenal cortex and neomycin sulfate on the list of drugs that could not be used and comments in favor of including dexphenfluoramine(?) and phenfluoramine(?) on the list.

In the case of adrenal cortex, the Agency decided that the substance should be included on the list that could not be compounded and we included it in the final rule because of our concerns about significant risks associated with the substance, both in terms of bovine spongioform(?) encephalopathy, BSE, and the associated risks of getting Creutz-feldt-Jakob disease and in terms of the risk of under treatment of serious conditions and our rationale is laid out in the final rule.

The Agency decided to postpone final action on

parenteral drug products containing neomycin, neomycin sulfate, because of the pendancy of various administrative actions concerning that drug. The preamble to the final rule indicated that neomycin sulfate may be added to the list at a later date.

Therefore,, the final rule contains 59 substances that may not be used for pharmacy compounding under the exemptions in Section 503(a) of the Food, Drug and Cosmetic Act. The list may be updated periodically if other drugs are removed from the market for safety reasons. We hope, of course, they aren't, but we will take that into account.

With regard to drugs that have been withdrawn for efficacy reasons, you may recall that at our last meeting, we mentioned three drugs that were nominated for inclusion on the list of bulks drug substances that may be used in pharmacy compounding under the exemptions in Section 503(a), but that had been withdrawn from the market for efficacy reasons.

Those three were betahistine, hydrochloride, cyclandelate and pentylenetetrazol. We deferred consideration of these because the Agency had not yet determined how we would handle drugs that had been removed from the market for efficacy reasons.

We have now concluded that we do not intend to devote Agency resources to compiling a list of drugs that have been withdrawn from the market only for efficacy reasons. Instead,

we have decided that we are going to only focus on drugs that are nominated for inclusion on the list of bulk drug substances that could be used in compounding.

The reason is that if a drug substance is a subject of an approved drug application for at least one indication, it can be used in compounding. If the drug substance is the subject of a USP or NS monograph, it can also be used in compounding. And if it doesn't meet either of these criteria, it can't be used unless it appears on the bulks list.

Therefore, we don't plan to develop a separate list of drugs that may not be compounded because they have been withdrawn only for efficacy reasons. Instead, if something is nominated for inclusion on the bulks list, the fact that it may have been withdrawn for efficacy at some previous date will be considered, along with other information and the other criteria that we have developed to make a decision as to whether it ought to appear on the bulks list.

That is the approach that we are planning to take for those three compounds. In November of last year, we published a guidance concerning our enforcement policy during implementation of Section 503(a). The committee has been provided with copies of that guidance. At our last meeting in October, a number of questions were raised about what was going to happen in terms of the transition period, while we were developing the many documents that we had to develop

to implement the statute.

This guidance recognizes that implementation of the new law requires us to develop many different rules and other documents that were not going to be in place when the statute took effect last November 21st. The guidance that FDA will not action to enforce certain provisions of the compounding statute until the related regulation or other document is completed.

For example, it says that FDA will not take action against a pharmacist who compounds a difficult to compound drug product until the agency promulgates the regulations required by the statute identifying what are demonstrably difficult drug products.

In this guidance, the Agency also establishes a specific transition scheme for bulk drug substances that are under consideration for inclusion on the bulks list. In the guidance, FDA gives compounders a one-year period to nominate new substances for the bulks list and that period was from November 21st, 1998, when the statute took effect, until November 21st of 1999.

We indicate that we will exercise enforcement discretion and will not normally take regulatory action against a drug substance that has been nominated during this period while that substance is being evaluated and as long as the substance does not appear to present a significant safety

risk.

For those substances that are nominated after November 21st, 1999, FDA will evaluate the substances, but they may not be used in compounding unless and until they are placed on a list if the compounding is going to qualify for the exemptions.

On January 21st, 1999, we announced the availability for comments of a draft standard memorandum of understanding to be entered into by the states that implements the provisions of Section 503(a), that addresses the interstate distribution of compounded drug products.

The comment period on this draft has been extended until June 1st, 1999, and we have received many comments on it, I think, over a thousand comments on this. So, we will be very busy analyzing the comments and doing what we need to do to get that out.

We will finalize the memorandum of understanding in consultation with the National Association of Boards of Pharmacy after evaluating the comments.

We are also working hard on the general pharmacy compounding implementing regulations and on the third list that we were directed to develop, the list of difficult to compound drug products that may not be used in compounding if it is to qualify for the exemptions under Section 503(a). We expect to present the first portion of the list of difficult

to compound drug products to you at our next meeting sometime this fall.

Finally, you should know that the day before Section 503(a) took effect, seven compounding pharmacies sued FDA in Federal District Court in Nevada, challenging the constitutionality of certain parts of Section 503(a) on First Amendment grounds. The suit challenged the constitutionality of the provision that states that to qualify for the exemptions under Section 503(a), a pharmacist may not advertise the compounding of particular drugs or classes of drugs, but may advertise the compounding service.

The suit also challenged the provision that for compounding to qualify for the exemptions, it had to be based on an unsolicited prescription. The court issued a temporary restraining order preventing FDA from enforcing these provisions, while the lawsuit is pending and the parties briefing the case said that the court can decide whether to impose a permanent injunction.

Before I turn this over to our first speakers on specific drugs, I would like to briefly mention that three drugs have been nominated for the list that we do not intend to present to you in formal presentations at this meeting.

The first is pentylenetetrazol, one of the bulk drug substances that was deferred after our last meeting because it had been withdrawn for efficacy reasons. Our Review

Division searched the literature for articles regarding the use of this compound in humans and was unable to find any information on it. The drug is apparently used in animal testing to induce seizures in animals so that anticonvulsant medications can be tested.

I checked with the International Academy of Compounding Pharmacists, who nominated this substance for inclusion on the list and they were unable to identify any literature on this subject. Therefore, we decided that we really had no basis for including on the list and really nothing to present to the committee on it. So, we won't be presenting anything further on that.

The second compound is chloramine-T. The Agency received a single nomination for this substance. The nominator reported the use of the substance by only one pharmacist at a rate of up to twice a year in a dental office for a root canal procedure. Our review of available data indicated that chloramine-T is an antiseptic agent and possibly an antibacterial. It has some uses in veterinary practices, which is not relevant here because the compounding exemptions only apply to human drugs and not veterinary medicines.

Very little literature could be found on chloramine-T. In reviewing the dental literature, chloramine-T is mentioned in a 1984 edition of Accepted Dental Therapeutics under "Root Canals and Cavity Preparations.

However, the current edition of the American Dental Association Guide to Dental Therapeutics, 1998, does not mention chloramine-T. Similarly, chloramine-T is not mentioned in a current endodontic text.

Based on our review of the literature, it appears that this is an outdated therapy for human use in dentistry and that its use is extremely limited. Lacking data on its historical use and with a lack of any evidence of widespread use, we don't believe that the substance should be included on the list of bulk drug substances and we don't intend to present any additional information about this to the committee.

The third compound that we are going to talk about is Peruvian balsam. We received a single nomination for Peruvian balsam. The nominator reported use of this ingredient by only one pharmacist in dermal and dental preparations amounting up to 16 ounces per year. Our review of available data indicated that Peruvian balsam is a gum resin used as a protectant in most cases. It is also an active ingredient in a product licensed as a biologic, used to test for allergic reactions to the balsam.

Because we could not document widespread use of this substance and because of its high potential for producing allergic reactions, CDER believes that this substance should not be consider for inclusion on the list for compounding and do not intend to present a formal presentation on this

substance at the meeting.

Of course, if anyone on the committee or any member of the public can supply us with additional evidence that any of these three compounds are widely used in pharmacy compounding or additional information supporting their placement on the list, we will be happy to consider it.

That concludes my prepared remarks. I can take any questions that you might have on what I have said before I turn to the first substances on the agenda.

DR. JUHL: Questions for clarification?

Hearing none, we will move to our first topic of conversation, dinitrochlorobenzene. There will be a series of FDA presentations by Dr. Vidra, Dr. Brown and Dr. Okun.

Please.

Agenda Item: Dinitrochlorobenzene

DR. VIDRA: Good morning.

As previously mentioned, my name is Dr. Jim Vidra, review chemist from the Division of Dermatologic and Dental Drug Products.

This chemical has several names; however, the easiest name to pronounce might be DNCB. The generic chemical name is 1-chloro-2,4-dinitrobenzene or 2,4-dinitro-1-chlorobenzene. This beige colored chemical has its physical and spectroscopic properties well established since its initial synthesis in 1875.

For you compounding pharmacists, its solubility properties include insoluble in water, slightly soluble in ethanol and soluble in benzene and ether and other organic solvents.

DNCB is considered stable at normal temperature and pressure conditions. During a fire, irritating and toxic fumes may be generated, such as hydrogen chloride, chlorine gas, nitric oxides, carbon monoxide and carbon dioxide.

DNCB is incompatible with strong oxidizing agents and alkaline bases.

Several published synthetic routes exist for DNCB. There are multiple impurities identified in bulk DNCB obtained from various sources. DNCB's impurity and yield may vary depending upon its route of synthesis.

This table from Wilkerson, et al., summarizes the impurities found in DNCB, sold by each of these six commercial sources. To briefly explain this table and using the Aldrich 98 percent pure DNCB as an example, the Aldrich sample contains 1-monochloro, mononitrobenzene isomer, 2-dichloro mononitrobenzene isomers, plus a dinitromonochlorobenzene isomer, other than the DNCB itself.

As a contrast, the ICN 98 percent pure DNCB contains only one isomer. The analytical method used was a gas chromatography mass spec analytical procedure. This method could not differentiate between the ortho, meta or para isomers,

simply due to the method of the mass spec itself.

To summarize the chemistry in Assessment 1, DNCB is well characterized physically and spectroscopically. It is stable under normal use conditions. The acceptability of any DNCB lot for compounding should be based upon knowledge of these two specific impurities, the 1-chloro-4-nitrobenzene, as well as the 1-chloro-2-nitrobenzene. These impurities could present carcinogenicity concerns.

The DNCB used in compounding could vary significantly from the DNCB used in literature studies due to its varying concentrations and types of impurities present. Altered clinical properties and toxicities could result from these variations.

Thank you.

DR. BROWN: My name is Paul Brown and I am a pharmacologist from the Division of Dermatologic and Dental Drug Products. And I will summarize safety information available from the literature on dinitrochlorobenzene.

Dinitrochlorobenzene and some of its possible impurities are mutagenic in the Ames assay and this mutagenicity appears to be due to direct interaction of dinitrochlorobenzene with DNA, since metabolic activation is not required. Dinitrochlorobenzene also induces -- is also genotoxic in human skin fibroblasts in vitro at low doses, similar to those that would be used in vivo.

Dinitrochlorobenzene did not induce tumors in rats or mice in an 18 month feeding study, although the dose of dinitrochlorobenzene in this study had to be decreased after four months for mice and two months for rats because of toxicity.

The carcinogenicity of dinitrochlorobenzene by the clinically relevant topical route has not been assessed and this is an important point since the outcome of carcinogenicity by the topical route may be very different than the outcome from the oral route.

Two possible precursors of dinitrochlorobenzene did cause significant elevations of tumors in mice in the same study in which dinitrochlorobenzene was evaluated.

Dinitrochlorobenzene is absorbed through human skin. For example, in one study, approximately 53 percent of radiolabeled dinitrochlorobenzene applied topically to humans was recovered in the urine over five days. In animal studies, dinitrochlorobenzene was shown to be irritating to the skin and cause the depletion of the important cellular protectant, glutathione in the skin.

In one study, it was shown that dinitrochlorobenzene activated the long terminal repeat promoter of the human immunodeficiency virus in transgenic mice, carrying this promoter.

This is a table that summarizes safety information about dinitrochlorobenzene, again, bacterial mutagenicity

was positive. Mammalian genotoxicity was positive, as measured in human skin fibroblasts. Dinitrochlorobenzene was negative for carcinogenicity for the oral route, while some possible impurities were positive. Topical carcinogenicity hasn't been evaluated, as I mentioned, and information on other aspects of dinitrochlorobenzene toxicity, such as chronic toxicity, reproductive toxicity, photocarcinogenicity have not been reported.

And the Assessment 2 that is in the written review also summarizes this information. Dinitrochlorobenzene is genotoxic and at least two of its potential impurities are carcinogenic in mice. Since other studies have not been conducted, teratogenicity or other toxicities cannot be excluded.

DR. OKUN: My name is Marty Okun. I am a medical reviewer in the Division of Dermatologic and Dental Drug Products. I am here to summarize what is known about the human safety and efficacy data pertaining to DNCB.

This slide has a cartoon of a poison ivy plant because the cutaneous reaction induced by DNCB is analogous to that induced my contact with poison ivy. Typical local side effects associated with DNCB application at the application site include burning, itching, blistering, crusting, urticaria, eczema.

The following systemic side effects have been

reported: fever and malaise, painful cervical lymphadenopathy, eczema at distant sites, not where DNCB was directly applied. Case reports also describe edema of eyelid and face requiring hospitalization and dyspnea characterized as of near tracheostomy severity.

There is limited long-term safety data available from use of DNCB. Our review indicates that a published follow-up of longer than six months duration is available for only 135 patients, most of whom were adults. No published reports on pregnancy outcomes are available. No cancer cases have been attributed to DNCB, but the duration and completeness of follow-up is not reported.

Pharmacists, physicians and other health care workers are potentially at risk for DNCB sensitization. Furthermore, although unreported DNCB treatment may sensitize to related compounds, such as nitrobenzenes, which are commonly used in agricultural industries. So, there is the potential for sensitizing workers in those industries.

If applied at home, concerns include the possibility of serious adverse effects from application without proper monitoring and possibly sensitizing of family members.

Our assessment of the human safety is that there are human safety concerns and since there is significant transcutaneous absorption in humans, systemic safety cannot be assured.

Before discussing the effectiveness of DNCB, briefly describing its target diseases as appropriate, we have here a clinical slide of a wart. Warts are scaly papules caused by infection with the human papillomaviruses. They cause cosmetic disfigurement, pain on walking if they are on the feet. They can interfere with manual tasks and are potentially infectious.

Safe, effective treatments are available, such as condylox, podofilin, salicylic acid, cryotherapy, lasers. All practicing dermatologists recognize that despite the availability of these treatments, warts are frequently recalcitrant to any or all of those modalities.

This is a clinical slide of two patients with alopecia areata, which is an immune-mediated non-scarring hair loss disease, which can affect patches of the scalp or the entire scalp, in which case it is called alopecia totalis, or the entire body, in which case it is alopecia universalis.

This disease causes cosmetic disfigurement and can also cause functional impairment, especially if eyebrows or eyelashes are lost.

For treatment of alopecia areata, there are treatments available that are reasonably safe and reasonably effective; corticosteroids administered a variety of routes and, again, a common experience is that despite the availability of these treatments, alopecia areata is frequently

recalcitrant to treatment.

Our assessment of the approved alternatives for treatment is that available approved products have been demonstrated to be safe and effective for the treatment of warts and alopecia areata and that some cases are recalcitrant to treatment, despite the availability of these alternatives.

This slide shows the dates of the first reported use and number of reports in the English language literature for a variety of indications that have been treated with DNCB, including warts, alopecia areata, melanoma, immuno-diagnosis and HIV. It is noteworthy, if you look at the year of last report, that the most recent studies of DNCB use for treating warts and alopecia are approximately ten years old.

Most dermatology texts and recent review articles caution against DNCB use, principally because of the positive results on an Ames assay, or warn about the hazards of mutagenesis or generalized sensitization reactions. Other immunogens that are evaluated, such as diphenylcyclopropenone, and squaric acid dibutyl ester rate more favorably.

Some pioneers in DNCB use have switched to other topical immunogens, principally because of these safety concerns, but, nonetheless, a few clinicians continue to use DNCB for treating alopecia areata predominantly for patients with more than 50 percent scalp involvement.

Our assessment of historical use is that evidence

of widespread use of DNCB is not apparent. Reports of DNCB use have declined in recent years, even in reviews of immunomodulatory treatments.

Typical method of use for alopecia areata and warts involves two phases. The first is a sensitization phase, a relatively concentrated solution; 2 percent in acetone is applied to normal forearm skin. The next phase, the elicitation phase, lower concentrations, ranging from .001 percent to 2 percent, depending upon the report is applied weekly or biweekly to lesional skin.

The concentration is titrated with the goal of inducing a brisk allergic response in lesional skin.

This slide shows a photograph of a hypersensitivity reaction, triggered in non-involved following a topical application of DNCB. You can appreciate the redness, the edema of the skin and microle vesiculation. This is the goal, to induce this kind of brisk allergic reaction.

In considering the efficacy of a proposed treatment for alopecia areata and warts, it is important to keep in mind the natural history of these diseases and, most importantly, that they can resolve spontaneously, depending upon the Lugia(?) Report, warts have been reported to resolve, about two-thirds of them resolve by two years of follow-up without any treatment and alopecia areata, the spontaneous resolution rates range from as low as 38 percent by five years to as

high as 94 percent by one year.

Nobody really understands the prognostic features that dictate the probability or the rate of spontaneous resolution of either of these two diseases.

The reviewed studies of DNCB for treatment of these disorders are largely uncontrolled or self or internally controlled or non-compliant patients are the control group. The problem with interpreting these studies is that without a control group of patients, it is very unclear how much improvement can be accredited to treatment effect, rather than to the spontaneous resolution that is possible with these disorders.

Nonetheless, assessing efficacy in alopecia areata, the percentage of patients with cosmetically acceptable response that persists off treatment ranges from 0 percent to 36 percent with a weighted average of approximately 9 percent and the duration of follow-up in these patients ranges from 3 to 18 months. It is unclear whether DNCB is more effective in those patients who are recalcitrant to the other treatments that we already mentioned.

The efficacy in warts, percentage of patients with complete resolution of treated warts ranges from 45 percent to a hundred percent, with a weighted average of 70 percent. Most studies were open label, with all warts treated. In the one internally controlled study where some of the warts

on the patients were treated and some were observed, the resolution of the treated warts was not statistically superior to untreated warts.

Again, it is unclear if DNCB is more effective in treatment of warts in patients who are recalcitrant to other treatments. We requested a consultative review by our colleagues in the Oncology Division to evaluate the effectiveness of DNCB in the treatment of recurrent melanoma and they concluded that the available studies are relatively small and non-randomized. They have short follow-up periods. They utilize several application techniques, such as topical or intralesional administration and that they are descriptive or anecdotal in nature.

Of note, no current standard oncology textbook recommends DNCB for treating melanoma. Further, our oncology colleagues reviewed the use of DNCB as an immunodiagnostic agent with the principal purpose of testing immune competence in cancer patients. They concluded that no well conducted randomized trials validating its use have been performed and, frankly, that the prognostic significance of reactivity is unknown.

A consultative review was performed by our colleagues in the Antivirals Division on the effectiveness of DNCB and HIV treatment. Their conclusions were that there was no consistent benefit on CD4, CD8, natural killer cell

count or progression to AIDS.

There was a statistically significant reduction in HIV viral load seen in one study of eight patients, but they felt that this was a fairly confusing result because these patients did not have any change in their CD4 count that is typically observed in response to decreased viral load.

They were concerned about potential interactions between DNCB and other approved anti-retroviral therapies and the potential interactions are unknown and potentially of concern.

Our assessment of the evidence of effectiveness is that there is limited evidence that DNCB is effective for the studied indications. With specific regard to alopecia areata, DNCB may provide an increase in hair of variable cosmetic quality, but such hair may be lost despite continued therapy or upon discontinuation of therapy.

And our conclusions are that we have concerns about placement of DNCB on the list of bulk drug substances for compounding. And these concerns include concerns related to safety, limited evidence of efficacy and in clinical use, DNCB has largely been supplanted by other topical sensitizers, because of the concerns about mutagenesis.

Thank you.

Agenda Item: Questions From the Committee

DR. JUHL: Do we have questions from the committee, either for Dr. Vidra, Dr. Brown or Dr. Okun?

MR. TRISSEL: One of the statements that was made was that there was a significant remission rate that occurs naturally. Does that include HIV patients, whose immune systems may or may not recover?

DR. OKUN: You are referring specifically to the remission rate of warts?

MR. TRISSEL: Yes. I am sorry.

DR. OKUN: There is no information in the published literature concerning the spontaneous remission rate in HIV patients with warts. The studies I cited to you were actually done before AIDS appeared in the community.

There is actually no published literature concerning the -- although it has been reported for treatment of warts in HIV patients, there is no published literature on the efficacy of DNCB in HIV patients, who have warts.R We looked rather thoroughly for that.

MR. TRISSEL: Elizabeth, do you have any input on that?

DR. MC BURNEY: I agree with Dr. Okun's comments that there are no published data on that and I would really like to reserve my comments to the other immunogens that we are going to be discussing later. I feel at this point that I would like to be able to have the drug available for those

few patients. There are two groups. One, the ones that he pointed out with alopecia areata with diffuse, extensive, greater than 50 percent of their hair loss. I think there has been data to show that using some of these topical agents in those patients, that perhaps we may be able to offer them something when they have exhausted all the other means.

That would be my concern for those particular patients. Then the second group of patients are those with very widespread warts, involving all the tips of their fingers, around all their nails, and these are patients that have severe immunosuppression, whether it be due to infection with the AIDS virus or due to iatrogenic inducement of loss of ambient system through chemotherapy agents.

These patients are frequently unresponsive to many -- to all the therapies that were listed. But as far as DNCB particularly, I would rather direct my comments to the other two immunogens that we will be discussing.

DR. LIEBMAN: Randy, we have two physicians or groups of physicians in Baltimore who use it. One of them is a pediatric dermatologist at Johns Hopkins and the other one is a community physician dermatologist, who also teaches on the faculty at the University of Maryland.

The general consensus is why do you use this because no one else seems to be using it. And across the board, the answer is we have exhausted all other possibilities. We have

gone through everything that we could have gone through and nothing has been successful. This is my last resort.

It would appear that it is successful because again and again they come up with new patients for it, knowing that it has potential downside, but somehow feeling, again, it is the only other -- if they don't have this, then they have nothing left.

I guess, somewhat with what Elizabeth said, at least they want the opportunity to have a fallback position. Their position is if you take it away, then I have got nothing to offer my patients.

MS. AXELRAD: Dr. Juhl, I was wondering if we could take questions on any of the information that was presented and then hear from the American Academy of Dermatology before we get into a sort of generalized discussion. It was sort of our feeling that the committee might want to hear the information on all three substances and ask questions about that and then discuss all three substances together after it has heard all the presentations, if that is okay?

DR. JUHL: I think that is good. Let's differentiate between items of clarification and questions for discussion. So, are there items of clarification?

MR. TRISSEL: One more.

DR. JUHL: Larry.

MR. TRISSEL: I just have one concern about the

use of apparently only published literature to establish use in the community because really you are establishing how much interest there is in publishing on this particular material, rather than how much it might be used. Now, on this case, of course, there are hundreds of papers in the literature. In others, there may be only a few, but rubbing alcohol is widely used, but I doubt if there is a whole lot of published literature in recent years on researching it.

So, I am not sure about the validity of establishing widespread use, using only published research articles.

DR. ALLEN: I have, I guess, a question. When we look at the conclusions -- and this is just kind of for my information as we look through all of these -- there were safety concerns, limited evidence of efficacy, et cetera, if we look at human safety, I guess I was wondering how that conclusion came because there are limited long term safety, but that is going to be common, you know, with a lot of these things; no published reports on pregnancy outcomes.

There is obviously not going to be any pregnancy studies. No cancer cases were attributed to DNCB. Pharmacists, physicians, other health care workers would be at risk for DNCB sensitization, but that is no different than working with doxyrubin(?), 5FU, et cetera, et cetera. I guess another couple of things, DNCB treatment may sensitize to related compounds. That could be true to other things.

If applied at home, concerns include, you know, family members. I guess my question is at what level are we looking at areas of safety and even efficacy, because there are studies where it has been efficacious, for the conclusions to be drawn that there are safety concerns and limited evidence of effectiveness? Where would be the line for not saying there is limited evidence of effectiveness and what would be the line for -- or what level of safety concern would be acceptable? Does that make sense?

In other words, where did the conclusions come from based upon what we have seen and read in our background materials?

DR. JUHL: Anyone want to comment on how the A led to B?

DR. DeLAP: If I could just comment briefly, and I think this is partly the broader discussion that Jane was just alluding to after we have looked at all the three compounds, I would just like to separate out the issue of whether a compound should be available period versus how it should be available because I think those are two different questions.

I think as we are looking at safety and effectiveness kinds of concerns and when a product becomes a kind of product that you would like to have more widely available with perhaps less safeguards and under the prescription or investigational mechanisms. Those are the kinds of things we have to weight.

What do we know about the safety? What do we know about the effectiveness? Is it still really more in the area of an investigational drug? Is there enough safety concern that that alone would make it something that should be out there?

So, these are all kind of judgment issues that we would like to really hear the committee's input on, but, again, I wouldn't want this to be a discussion of whether it is something that should be available or not available, so much as if you think it is worth having, then I think it becomes more of a discussion of how it should be available, as opposed to, you know, a "yes" or "no." Is it appropriate for compounding or is it more appropriate to still be under INDs with all of the things we can do to try and make that as user friendly as possible or should it be -- you know, should it be prescription?

DR. JUHL: Sarah.

DR. SELLERS: I would just like to clarify that this -- for both indications, these are being used chronically, so patients will be seeing long term exposure to this agent potentially.

DR. JUHL: Is that your experience, Dr. McBurney?

DR. MCBURNEY: No, it is not at all. What we usually do is we try to induce, as Dr. Okum showed, 2 percent solution on the skin and induce an allergic reaction or an immune reaction. Then we paint it on the individual lesions, say the warts

or the area of loss of hair of alopecia, depending from once a week to as frequently as twice a week or even three times a week in some patients, generally on a once a week basis, until we get a response or until you decide that there is no response.

But this is not done over a year's period. This is done over weeks or months, rather than in terms of years. Then it is usually discontinued. Now, if there is a recurrence, there may be a decision to reuse that therapy later, but it is not like, for instance, you would take a heart medication for the rest of your life or high blood pressure medication. It would be used in a time-limited fashion.

DR. JUHL: Okay. I don't think we will abandon the issues by going on to the next drug. So, let's do that.

Dr. Rodriguez.

DR. RODRIGUEZ: We heard about the drug being, quote, unquote, absorbed from the skin and 53 percent in the urine. How long does it persist in the body? I am just trying to think in terms of the -- we know some drugs that may stay for weeks after that or something like that or is this an acute type sort of exposure and then the drug sort of disappears.

DR. VIDRA: The data that I talked about with the 53 percent, that was in the urine after five days. So, they looked -- in that particular study, they did look over, I think, a 24 hour period. I think the majority of the drug

was eliminated early on, like in the first 24 hours, but, again, that is 53 percent in urine. In that particular study, they didn't look at the PCs(?) or anywhere else. They don't know where the other 47 percent is.

Since it does interact covalently, some of it might be bound in tissue and it might not get out in the urine.

DR. MC BURNEY: I would like to just point out one thing that was mentioned in the presentation, that we have safe effective treatments for alopecia areata and they list underneath that corticosteroids intralesionally, meaning they are injected under the skin topically, which would be a lotion or a cream, and then systemically.

I must state concern about it being listed as safe, effective, systemic steroids because we are all familiar with the many side effects and that particularly is a problem with long term use in our pediatric patients of long term use of systemic steroids.

DR. JUHL: Okay. Let's move on to diphenylcyclopropenone. Dr. Hathaway is doing the chemistry and then Dr. Brown and Dr. Okun are back for their presentations.

Agenda Item: Diphenylcyclopropenone

DR. HATHAWAY: Good morning. I have been asked to speak about what is known about the chemistry of diphenylcyclopropenone, also known as DPCP. Diphenylcyclopropenone is a low molecular weight, small ring

organic compound, whose physical and spectroscopic properties have been described in a number of published reports in the literature.

It is possible to confirm the identity of the bulk material from various sources by comparison of the properties and the spectra. The stability of diphenylcyclopropenone has been evaluated by examining the known chemical reactivity as published in the literature. DPCP is unstable to heat at temperatures near its melting point, around 120 degrees celsius.

Carbon monoxide is emitted leaving behind diphenylacetyline and other unidentified products. DPCP is also light sensitive and appears to decompose in a manner similar to that of heat. Note that DPCP is affected by light of any type, natural or artificial and including ultraviolet light.

DPCP is unstable in alcohol solutions of base and rapidly decomposes to form a number of products, some of which are unidentified. It appears to be stable in neutral or acidic solutions of alcohol. It is not soluble in water. And DPCP is also chemically reactive, forming addition products with a number of materials.

There are several published synthetic methods for producing DPCP or similar compounds. There is also a second solid form known, the monohydrate, which may come into play

regarding identification or amounts. There are also several commercial suppliers. However, it is not known what methods are in use for production of DPCP by these suppliers.

Literature reports are primarily concerned with the methods of synthesis and little or no information has been reported regarding the identification and characterization of any synthetic impurities or degradation products in the bulk chemical.

Lastly, quantitative methods of analysis have not been published in these literature reports. Thus, we are unable to determine how well, if at all, impurities are measured.

This is our assessment for the chemistry. The physical and spectroscopic properties have been adequately established in the published literature. This material is unstable to heat and light under a variety of conditions. It is also known to be unstable in alcohol solutions at basic pH, thus, limiting a choice of compounding material.

It may also be unstable due to reactions with other materials. Numerous sources and methods of production indicate that the impurity profile may differ with the source and the uncertainties of analysis may be a concern here.

Thank you.

DR. BROWN: Now I will summarize some safety information that is available from the literature on diphenylcyclopropenone. Diphenylcyclopropenone is

mutagenic in the Ames assay but only in the presence of light. Alpha, alpha-dibromodibenzylketone, which is a synthetic precursor and, therefore, a potential contaminant of DPCP is mutagenic in the Ames assay both with and without metabolic activation.

The potential for absorption of diphenylcyclopropenone is not clear, although diphenylcyclopropenone was not detected in the serum or urine of humans treated topically in the only reported study. The techniques used in that study did not exclude the possibility that diphenylcyclopropenone was rapidly absorbed and metabolized.

This is a table then that summarizes safety information from the literature about diphenylcyclopropenone. Again, it was mutagenic in bacteria with light and, unfortunately, other aspects of toxicity have not been reported in the literature.

Then, again, the Assessment No. 2 in the written review also summarizes the information that diphenylcyclopropenone is photogenotoxic. But given the lack of additional studies, it is not known what toxicities diphenylcyclopropenone may have or whether it may be teratogenic.

This slide shows a list of the recent reports describing side effects associated with the use of DPCP and

several are listed here. There have been more published reports of side effects associated with DPCP use and for either DNCB or squaric acid, which will be discussed next.

Our assessment of human safety is that there has been limited characterization of human safety. There have been local side effects described, typically a burning, itching, blistering, clustering, urticaria and eczema, analogous to what is seen with the DNCB. A less commonly vitiligo is induced, which sometimes can be persistent and also something called dyschromia in confetti, which is hyper-pigmented areas with islands of hypo-pigmentation. That also can be quite persistent.

In reviewing the literature, the following systemic side effects have been reported, fever and arthralgias, disseminated bullous erythema multiforme, which is a skin disease characterized by a bruise-like blistering, wing-shaped lesions scattered over the body and generalized vitiligo and generalized eczema, vitiligo and eczema not confined to the sites where the DPCP was applied.

Pharmacists, physicians and other health care workers are at risk for DPCP sensitization. There is a report that three out of five medical and nursing staff members developed severe local dermatitis and irrigation of the eye and nose and generalized pruritus from incidental exposure to DPCP.

Apparently, these staff members experienced symptoms simply by entering a room where DPCP had recently been dispensed or mixed up.

If applied at home, sensitization of family members is possible. There is a case report, which attributed incidental exposure of DPCP as the cause of a case of eczema and persistent vitiligo in the wife of an alopecia areata patient being treated with DPCP. In that case report, parenthetically, DPCP was applied in the clinic. So, this was exposure from the material that had rubbed off of a patient after he had gone home and vitiligo had been persistent.

Our assessment of the approved alternatives for treatment, if I may follow up on Dr. McBurney's comment, we agree that a long term systemic, corticosteroid treatment is not safe and it is on this list as reasonably safe when referring to comparatively short burst in papers of a month's duration, which has been used in literature to reverse alopecia areata. Used in that manner, you can avoid many of the side effects associated with long term use, but, clearly, a long term use is not safe.

We have already discussed previously that there are safe, effective treatments available for warts and I will just reiterate that despite the availability of these alternatives, there is no question that some cases are recalcitrant to all of these treatments.

Historical use, our assessment, the first reported use of DPCP for treatment of alopecia areata was 1983. There are at least 18 reports in the literature on using DPCP for alopecia areata. Five reports use this treatment in warts. Evidence of widespread use is not apparent. The point is well-taken that the published literature does not necessarily capture the totality of the clinical experience, but that is the basis of our review. This is a summation of the published reports.

The typical method of use of DPCP is -- it is applied in the provider's office. A relatively concentrated solution is used to sensitize to uninvolved skin and a much more dilute solution is used to sensitize -- after sensitization has occurred, much more dilute solution is applied to trigger reaction in lesional skin.

The largest study characterizing DPCP use in warts, 134 patients were treated for eight weeks and the response rate was 37 percent; all warts resolved, 37 percent of the patients had all their warts go away and 13 percent, at least some of the warts resolved.

This was an open label study.

Assessing the effectiveness of DPCP in alopecia areata, which has recently been reviewed in a review article and their conclusion was that the response rate, which in their assessment included cosmetically acceptable or partial

regrowth. The response rate ranged from 9 to 85 percent, with a weighted average response rate of 58 percent.

In the larger study, response rate was 50 percent, but the relapse rate is approximately 50 percent. As with the DNCB, it is unclear if use of DPCP is more effective in patients who are recalcitrant to other treatments.

Most cited review studies were uncontrolled or self or internally controlled. In a randomized, placebo-controlled study, no significant difference in outcomes was observed between patients treated with DPCP and patients treated with placebo.

Our assessment of the evidence of effectiveness is limited evidence that DPCP is effective in the long-term treatment of alopecia areata or warts. Treatment of alopecia areata may provide an increase in hair of variable cosmetic quality during treatment. This hair may be lost if therapy is stopped.

In our conclusions is that there may be variations in the impurity profile of bulk DPCP. There is comparatively limited evaluation of the safety of DPCP, specifically with respect to long term toxicity, dermal and systemic, reproductive toxicity, carcinogenicity and photocarcinogenicity, especially given that there is a positive assay in the presence of light and microsomes.

There is variable effectiveness with limited

evidence of long-term benefit.

Thank you.

Agenda Item: Questions from the Committee

DR. JUHL: Questions of clarification for our speakers?

Bill.

DR. RODRIGUEZ: I have some questions. Maybe I misunderstood it, but there is quite a number of reports of, quote, unquote, side effects in here of recent vintage. That suggests to me that there is, quote, unquote, an objectionable ratio of side effects to use or aquatic use of the medication. So, I was wondering about that part.

The other one that I was wondering about is in some of these studies where it has been used for alopecia areata, have they reported the number of side effects in those groups because at least you get a general idea. I am not sure that -- obviously, this is not my field, but I am just looking at it from the scientific point of view.

The third thing is a study that compares 20 versus 35, the power of that study must have been very, very, very low. You know, from other areas of the literature you have anywhere within 9 percent and 50 percent. So, again, I have questions about random trials that are that small.

I am not -- I don't use this medication, but I am

just raising this concern from a curiosity point of view.

DR. OKUN: Your points are certainly well-taken. It is very hard to assess from a review of the literature what the denominator is. In other words, how many patients are using DCPC and not having any problems. Nobody is going to write up a case report of a patient who doesn't have an adverse event.

All we have a sense of are the numerator, rather than the denominator. Your point also about the randomized trial is also quite valid. In general, I am not sure how much weight you can put on a single trial with relatively small numbers. Again, our responsibility is to look at what is out there.

This is the only randomized placebo controlled trial. Everything else was open label.

DR. LIEBMAN: I am concerned about the fact that you keep talking about long-term use, long-term use. Repeatedly, you have heard Dr. McBurney say it is not used long term and with respect to hair loss, if you discontinued the medication. Is that not true with menoxidil(?) also? And is that not true of rotepropecia(?)? Would you say is that then a downside of those two drugs also or is that just a reality that says when you are taking hair growth medicine, hair grows sometimes when you stop taking the medicine.

The hair that has grown tends to not continue growing.

I mean, it sounds like it is presented as if that is bad. I think that is just part of the drug. It goes with other drugs in the same light. The same kinds of drugs give those same kind of side effects.

DR. OKUN: I think Dr. McBurney has characterized the natural history of alopecia areata very accurately. Individual episodes may not necessarily be very long and individual treatment may only need several months to reverse the loss.

However, my impression is that alopecia areata is a long term disease in which there are periods where disease activity has remitted and periods where that exacerbates. Each individual treatment duration may be several months, but most patients who were in the literature, reviewing their case reports, they may need several treatments over the course of an extended period of time as their disease waxes and wanes in severity.

DR. LIEBMAN: You are right, but you keep saying "it may," as opposed to there is documented evidence that it does cause. My concern is that there is kind of the, I guess, implied threat -- and I know that is not what you are saying -- that maybe if you use it long term, maybe you will have side effects.

To me, that skews it a little bit and I am not sure that is not what you are trying to do.

MS. AXELRAD: If I could just make a comment and you might respond, but, basically, I think for approved drugs, for drugs that are approved treatments that we have reviewed, they have been put through an extensive battery of tests to show what the consequences are of whatever use it is going to be put to on the label.

There are, you know, reproductive toxicity tests, carcinogenicity tests and all that -- our experts, you know, elaborate on that, but basically these compounds, we don't have any of that kind of evidence on. I think that is the contrast between the approved drugs and the ones that we are considering here.

DR. O'CONNELL: Dr. O'Connell, Department of Dermatology and Dental Drug Products.

That is essentially what I was going to point out. With an approved drug, there is informative labeling for the physician and the patient so that they can make a judgment, based on the evidence for efficacy and the strength of that evidence. And the known risk, true, all risks aren't known at the time drugs are approved, but at least the risks that are known at the time of approval and then labeling is updated.

But the other point I would like to make, since I am filling in for Dr. Welkin, I am going to steal a statement that he likes to point out to us when we discuss things. The absence of evidence is not evidence of absence and the

fact that we don't have this information certainly, I think, weighs at least as heavily as the facts would weigh if we had evidence that they were unsafe. See what I am saying? We don't know is the bottom line.

All we have is what is published, but that doesn't mean that because things aren't out there, that they are not occurring, because it is not published that it is not occurring.

DR. JUHL: I believe we are bouncing back and forth between safety questions and questions of effectiveness that we don't have good information for. I believe if we took Assessment 6 that Dr. Okun presented to us, it says that there is limited evidence of long-term effectiveness. There may be a variable cosmetic quality of the response and the hair may be lost if therapy is stopped. We could put any of the drugs that are used to treat that malady in there and have the same criticism be made of them.

The difference between those drugs that had been labeled as safe and effective, it is more on the safe part and the effective is with quotes around it, I guess, the regulatory meaning of "safe" and "effective."

So, I think we really have a difference in safety and a safety in chemistry and controls and so on that we have with commercial products as the major focus here. We aren't going to have good information. We are not going to have the kind of information you folks are accustomed to looking

at, but we are dealing with those patients that didn't fall within the whatever percentage of response. The question we will have to deal with then is is there a way to make other alternatives available for people, but above all, we don't want to do harm and it would be nice to know we had some indication that they worked.

Are there other questions or clarifications? Yes, go ahead.

DR. PECK: I will be probably be going back to this on other compounds. It is a little of a concern to me about multi-commercial sourcing. Then we get into the second thought about poor analytical procedures to evaluate the particular compounds.

The statement about well-characterized physical properties, I am not sure that there are well-characterized chemical properties. Some are mentioned, but it is not that complete.

A good remark is made about the impurity profile may vary with source. That, in turn, will carry over to the patient response if the material is not, quote, as good as one would like to have a clinical application.

So, my thoughts are about the inability to have a good feel about sourcing.

DR. JUHL: We shall then move to our third drug in this category, squaric acid dibutyl ester. We have the

same cast of characters from the Agency, please.

Agenda Item: Squaric Acid Dibutyl Ester

DR. HATHAWAY: Again, I am Steve Hathway, Derm and Dental Drug Products. Now I am speaking about squaric acid dibutyl ester.

Squaric acid dibutyl ester is a low molecular weight small ring organic compound, similar to DPCP. And the physical and chemical properties resemble those of carboxylic acid esters. A number of reports published in the chemical literature have established the physical and spectroscopic properties of this compound. It is, therefore, possible to confirm the identity of this material from various sources by comparison of its properties with these known values.

The stability of SADBE has been evaluated by examining the known chemical reactivity as published in the literature. Squaric acid dibutyl ester does not appear to have sensitivity to moderate amounts of heat or to exposure to light, though its structure suggests that there may be a photochemical reactivity.

Squaric acid dibutyl ester has been reported to be unstable in water solutions. This hydrolytic activity varies with the pH and is fastest in basic solution. The hydrolysis also occurs in acidic and neutral pH.

About the synthesis, there are several published methods for synthesis of squaric acid dibutyl ester and related

compounds and there are also several commercial suppliers. However, it is not known what methods are in use for the production of this compound.

The literature reports are primarily concerned with the methods of synthesis and there is little or no information reported regarding the identification or characterization of any synthetic impurities or degradation products in the bulk compound.

Finally, quantitative methods of analysis have not been published. They are typically semi-quantitative in the published literature. Thus, we are unable to evaluate how well, if at all, impurities are measured.

Lastly, our assessment of the chemical properties and behavior, squaric acid dibutyl ester's physical and spectroscopic properties are adequately established in the published literature. The material is stable to heat and light under normal conditions. It is known to be unstable in aqueous solutions at all pH's and also in solutions where there is a trace presence of water and, thus, this would limit their choice of vehicle.

And numerous sources and methods of production indicate that the impurity profile may differ with the source and the uncertainties of analysis may be of concern.

Thank you.

DR. BROWN: I am Paul Brown, still. I will summarize

the safety information available from the literature on squaric acid dibutyl ester. Squaric acid dibutyl ester is not mutagenic in the Ames assay and it does not cause transformation of hamster kidney cells in vitro.

There are at least two synthetic precursors of squaric acid that are potential contaminants of squaric acid dibutyl ester, hexachlorobutadiene and tetrachloro-2-cyclobutene-1-one. Hexachlorobutadiene is carcinogenic in rats and tetrachloro-2-cyclobutene-1-one is carcinogenic in mice.

Squaric acid dibutyl ester has been shown to penetrate human and mouse skin in in vitro experiments and experiments in hamsters have shown that the dibutyl ester of squaric acid is a more potent sensitizer than the diethyl ester, demonstrating that the different esters are not toxicologically equivalent.

Then this is a table that summarizes the safety information about squaric acid dibutyl ester. Again, the bacterial mutagenicity is negative and information on other aspects of squaric acid dibutyl ester toxicity has not been reported, although there may be some carcinogenicity of potential impurities.

Then Assessment 2 in the written review also summarizes the information that two potential contaminants are carcinogenic and given the lack of additional studies,

other potential toxicities and teratogenicity of squaric acid dibutyl ester are not known.

DR. OKUN: Our assessment of the human safety of squaric acid dibutyl ester is that its characterization is limited. There have been side effects described in the case reports. Some are local, manifesting as blistering, itching, eczema. That is fairly common; less commonly, pigmentary changes occur.

The following systemic side effects have been reported: fever and arthralgias, severe generalized dermatitis, distant local dermatitis, generalized pruritus without dermatitis. Clearly, these side effects do not necessarily have to be localized just to the site of application.

We have a clinical picture of a typical blistering reaction with squaric acid dibutyl ester. I think in this case, the health care provider has overshot his or her goal of inducing allergic reaction. This is a little too much. It is hard to titrate.

We have already covered this. Approved alternatives for treatment are the same as with the DNCB and DPCP. So, I think we should skip this.

Historical use of squaric acid, the first reported use in 1980 for treatment of alopecia areata and it has been used as an experimental treatment alternative for alopecia areata, 14 reports in the literature and for warts there is

one report.

Evidence for current widespread use is not apparent.

The typical method of use, again, is analogous to what was described for DNCB and DPCP, a sensitization and then an elicitization phase.

Review of its use for treatment of alopecia areata response rate, which includes a cosmetically acceptable or partial regrowth rate, ranges from 29 to 87 percent, with a weighted average of about 59 percent. In the largest study, the response rate was 65 percent, a relapse rate of 50 to 70 percent, even with continuation of treatment.

Again, these studies were predominantly open label, internally controlled.

It is unclear if squaric acid is more effective in patients who are recalcitrant to other treatments.

The same study that was mentioned earlier for the DPCP, another arm compared efficacy of squaric acid against placebo and the numbers are comparatively small, 44 patients on squaric acid, 20 patients on placebo; no significant difference in outcomes.

Our assessment of evidence of effectiveness, limited evidence that squaric acid is effective in the long term treatment of alopecia areata or warts. Treatment may provide increase of hair of variable cosmetic quality during treatment. The hair gained on treatment may be lost even with continuation

of therapy.

Our conclusions are that there may be variations in the impurity profile of bulk SADBE. There is limited evaluation of the safety in terms of long-term toxicity, both dermal and systemic, in terms of reproductive toxicity, in terms of carcinogenicity and the photocarcinogenicity.

There is variable effectiveness with limited evidence of long-term benefit.

Thank you.

Agenda Item: Questions from the Committee

DR. JUHL: Additional questions of clarification?

Elizabeth.

DR. MC BURNEY: I don't want to get technical and bogged down in studies, but I would like Dr. Okun to elaborate a little bit because the study you mentioned by Antonelli Tosti in 1986 that compared the difference immunogens, that is, the topical agents versus placebo, I believe that particular study dealt only with very patchy alopecia areata. There was less than 40 percent of the hair loss.

The real use of these agents are in patients that have very widespread alopecia, recalcitrant alopecia areata. I certainly would agree with your conclusion and that is that people with very limited areas of alopecia areata are the patchy areas, say, one to ten areas less than the size of a dollar, a silver dollar, are going to have a normal response

of resolution. Whether you treat them or not, they are going to get better.

I certainly concur with your point, but I do think we need to realize that there is a smaller subgroup out there of patients with very severe widespread non-responsive alopecia areata. I want to make that point and please correct me if I am not portraying that accurately.

DR. OKUN: My recollection is that most of those patients in that study did have comparatively little hair loss. I am trying to recall the details of the entry criteria. I can't remember off the top of my head.

Your point is well-taken. I am not certain that one can be confident that the responsiveness in limited cases is substantially different than responsiveness in widespread cases. But certainly it is a small study. I am not sure how generalizable the results are. That is what is out there.

MR. CATIZONE: Mr. Chair, I have a question of clarification but not to the technical aspects of the products, but more in general of process and the committee's responsibility. So, I don't know if you want those now or at the end of the discussion?

DR. JUHL: Is it something that someone could answer in two sentences or less or will this lead to a discussion? I guess I will let you use your judgment.

DR. OKUN: More than two sentences.

DR. JUHL: Shall we save it for our discussion session?

I would like to move now to the presentation by the American Academy of Dermatology, nominators of these compounds, Dr. William Rosenberg, professor in the Departments of Medicine and Preventive Medicine at the University of Tennessee.

Agenda Item: American Academy of Dermatology Presentation

DR. ROSENBERG: Thank you very much. I appreciate the chance to represent the American Academy of Dermatology. I would like to say that I also serve on the Medical Advisory Board of the Alopecia Areata Foundation, which is a patient advocacy group of people concerned with this disease, which can be devastating to many of them. They have asked me also to speak for them in support of the wish that the practicing community will still have the opportunity to use this treatment when possible.

I want to make a few comments, a little bit of historical review and then be available, I hope, to answer questions from the group.

Of course, benefit to risk is at the heart of regulatory decision-making and in terms of the benefit here, I would point out that we are dealing, certainly at the alopecia areata aspect of it, with some patients, who really carry

a very heavy burden of disease. The pictures that were shown of widespread disease are not unusual. People will lose more hair than that.

Many of them are young and terribly upset by what they face with this during the difficult periods of adolescence and childhood. Dr. McBurney, I think, speaks for most of us, who are interested in practice in this area, that systemic steroids are not an acceptable treatment for alopecia areata.

The hair that grows with systemic steroid comes right out after you stop this systemic steroid, which is not the case with this kind of treatment. And the potential side effects and relapsing and remitting disease are well-known and almost the worst thing about the corticosteroids by mouth is that they almost always work while you are taking them. So, there is a great temptation for patients to want to keep taking them, keep taking them while they do themselves further harm.

Most of us who are interested in this disease do not consider that safe and effective. Intralesional corticosteroid is safe and effective, small shots of atriumcynelone(?) asetinide(?) suspension, usually somewhere around 5 milligrams per ml, sometimes 10, will grow hair in a very limited area. This has a limited applicability to people with small area of alopecia areata. It is not suitable for widespread areas.

So, this is a treatment that in terms of alopecia areata, that we would miss very much if we didn't have it. Just a little historical review about this, I suppose I have more experience with this treatment than anyone else. I was, to my knowledge, the first to have used it and it was a patient 25 years ago or a little bit more, the wife of a surgeon, whose office was around the hall from where I was practicing in the sixties, 30 years ago, who had long time alopecia areata and was taking systemic corticosteroid on her husband's prescription.

We got to be talking about it and I told him that intralesional steroids had been introduced since she had been started on that other treatment and that these were much safer. She was a grown woman. She taught high school French. So, we began a relationship with this patient where I would see her two or three times a year and inject five or six new spots every time.

One day in the office after five or six years of this, she said to me, Bill, why is do you think that I have to keep coming in and getting these new spots treated? Why do I keep getting it? And I said to her, Betty, I said, probably the more interesting question is is why most people who get alopecia areata recover spontaneously and have it again maybe once or twice or frequently never again, but don't have the trouble that you have.

And she said why do you think that is. I said I don't know. I said, the trouble, of course, is these lymphocytes that appear around the hair and then the hair goes away. We don't know what the lymphocytes are attracted to there. I said maybe what it is, most people the lymphocytes are able to get the trouble away and then the hair can regrow and there is no more reaction.

And she said is there any way to get more lymphocytes there? I said, well, actually there is. There is an allergist who works in the same office, has a product called DNCB that he puts on people's arms. They are supposed to become sensitive to it and it will bring lymphocytes in most people.

She said, you want to try it? I said sure. So, we put some -- sensitized her to DNCB and put some weak DNCB on her alopecia areata and it grew hair and we reported that or presented her case to a -- at the time, the Archives of Dermatology used to present the transactions of dermatologic society meetings. Dermatologic society meetings worldwide are always -- frequently, one brings a patient to the society meeting and the members of the society see the patients and discuss their case and then those cases always used to be reported in some of the journals.

So, this single case report, which was not really a case report, but what was the transactions of a meeting of the Memphis Dermatological Society was published in the

Archives of Dermatology. Rudolph Hopley, a dermatology professor in Germany, read this and began doing this on an organized and thoughtful and extensive way.

We began also to do some larger studies. Hopley then told us that the West German regulatory agency told him not to use it because of the Ames test, but said that these other -- he said that the other two drugs -- first, the SADBE, later the DPCP, had passed that review and that is what most of us started using.

So, on the basis of, as I say, 25 or 30 years and lots of patients personally, I can tell you that it would be very hard to not to have this to offer to patients who come in with this terrible disease. One of the sad things about this kind of disease is parents and patients have been told that it is due to stress and dysfunctional family life and so forth. And that is not true either.

Whether it is autoimmune disease or whether there is actually some antigen there in the form of a virus, it is not at all clear. Hopley feels that it is autoimmune disease and SADBE brings suppressor cells. I still in my heart think that there is some evidence for a virus and the related disease vitiligo also, there is evidence of a virus.

So, the issue is unclear. The fact is that this treatment is helpful for a lot of patients. I brought along a statement from Jim Davis, who is a pharmacist who has been

mixing it for me for 25 years. I asked him for that a week or so ago and he said he would, but his wife was ill. He was going to take her to Florida for a couple of weeks to try to recuperate and he left a statement, which I am not sure I understand exactly, but from the point of view of the practicing pharmacist, this is not only something that he can do in the office, but that he feels is important to him and it has been a very gratifying aspect of his career as a compounding pharmacist, the ability to work with these patients.

DR. JUHL: I wonder if I could ask you to clarify. You said that this treatment -- and I assume you talk about the method of the treatment, but we have three compounds. Could you clarify which --

DR. ROSENBERG: I have not used DNCB, again, as Dr. McBurney said, many of us have not used DNCB for a long, long time, since really Hopley first presented these other two chemicals to us. So, my experience is with SADBE and DPCP, apparently is a little more stable in acetone, although I am not sure of that. We have both of them available at the pharmacy.

Patients will sometimes become tolerant of one and need to be sensitized to the other, but I would hate to lose both of them. In terms of the efficacy statement, it does not have a commercial sponsor. It has not had that kind of

a study, but Hopley has published numerous pictures and we have seen the same treating one half the head and the hair grows on that half of the head and not on the other half.

Then the other areas will grow hair sometimes, it seems that -- in the same that in the same way they treat few warts successfully and sometimes they all go away, the immune system is certainly active in this disease and it has become now legitimate apparently in clinical immunology to talk about immune modulating substances, which means that it is a very complicated system and we don't exactly know what we are doing but sometimes benefits accrue and I guess we can use that kind of a term here in terms of whether it is an immune suppressor or an immune adjuvant. Certainly, in warts most of us think it is an immune adjuvant.

DR. JUHL: I wonder if I could ask you to offer an opinion on the quality of science, at least as we would like to have -- we would like to have all the answers -- doesn't seem to be there.

The question I have is: Is it possible to know more if we had a better system of collecting information or is this illness so unusual and so patient specific that it is hard to do research on or is it the lack of funds to do research on? But from our perspective, we need to decide if they are to be available or to recommend whether they be available and if so, how they would be available.

I am wondering if a more systematic collection of information would yield anything, either in terms of how well the drugs work or how safe they are.

DR. ROSENBERG: I am sure that could be done in terms of priorities. I am sure it would probably not be on anybody's list. As I say, it has no commercial sponsor and I think the -- I would be surprised if the NIH wanted to do a placebo study. As far as the efficacy is concerned, I think -- again, as Dr. Okun pointed out, the Tosti study, the power was too low in a disease with a high spontaneous cure rate or recovery rate to show a benefit over placebo.

In terms of efficacy, I would say that the practicing community of dermatologists and the medical board of the Alopecia Areata Foundation, which presently includes the dean of the University of Rochester College of Medicine and a couple of very -- really distinguished serious scientists. The efficacy is there. Dr. McBurney can speak from her perspective.

I think there is no question -- certainly, it doesn't work every time, but certainly it will help some people. In terms of the safety, I think the fact that this community is concerning itself with safety must be welcomed by everybody, the Academy of Dermatology, the Alopecia Board, all the patients and all the practicing communities. That is something that none of us wish to treat patients with unsafe products.

DR. JUHL: I guess in a way I consider for lack of other sponsors, the practicing dermatologists and compounding pharmacists to be the commercial sponsors of this product. What I would like to have a feel for is could we get more information from that group if there was an organized effort amongst them to do so.

DR. ROSENBERG: I don't know how it would be organized. The Alopecia Areata Foundation raises funds and it has been giving away -- making grants of two to three hundred thousand dollars a year, but -- and, again, the board looks -- reviews the requests, but the feeling has been that science-based research, laboratory work into a function -- interreactions between the immune system and the hair follicle and some aspects of hair regeneration are more likely to move this forward and then would be a large clinical study.

There have been requests for monies to do these kind of clinical studies and they get low scores so that they have not been done. We have been looking for an animal model and there now are animal models and which may or may not be exact, but, I mean, it is that type -- in one very recent study, one of these agents worked in one of the animal models. I am sorry I don't have that reference. I don't know if you saw that.

DR. JUHL: I guess I am more looking from a practical point of view, from our decision-making process, would the

academy be interested in sponsoring an IND such that when people are using this amongst your association of dermatologists, they would have a standardized product that comes from one manufacturer that we know more about, that there be a standardized collection form of adverse effects and a registry almost.

DR. ROSENBERG: I couldn't speak for them. I am not sure that I recall that kind of activity ever having been done.

DR. JUHL: I don't think it has, but I am asking would that be of interest to the academy?

DR. ROSENBERG: I don't know. For those of us that care about this disease, of course, many of our colleagues will refer patients so that I think in terms of everyday practice, lots of people could get along without it, but for the patients with alopecia areata, it is really necessary that there be some doctors who want to do this and some medicine that they can look to with some hope. They really would like to be able to continue this kind of treatment. They find it helpful and we find it helpful.

DR. JUHL: I have no argument with that. The patients have to come first, but we don't have enough good information. We could use more information. I guess I am wondering is there the will amongst --

DR. ROSENBERG: As I say, in terms of safety, we

would yield absolutely to your judgment. I certainly would and I am sure everybody would. In terms of efficacy, I think we could -- if you would accept that publication of a randomly controlled evidence based placebo study in a refereed journal is the only kind of evidence, that -- and some people think that about a lot of things, we just don't have that. The nature of this would make it extraordinarily hard.

It seems to me that reasonable people looking hard, of a panel of reasonable people looking hard at the published -- even the published material, not just anecdotal, the pictures of patients and the weight of evidence that these things work in alopecia areata would conclude that they are effective for growing hair in a certain percentage of these patients.

I think -- I would not accept evidence-based criteria, as they now exist in the practice of medicine for the refereed journals and so forth and so forth. We are talking about a sort of a little by -- backwater area here of medicine that for those of us that are in it and have it, it is very important. I truly think that I would not -- would urge this committee not to assume that these things are not effective.

DR. JUHL: Other questions for Dr. Rosenberg?

Dr. Sellers.

DR. SELLERS: How many patients are affected by this and what is the breakdown of peds to adult patients?

DR. ROSENBERG: I don't know that answer. It is

a high -- of those that want treatment, it is a high percentage of adolescents and some children. I should know the answer but I don't.

MR. CATIZONE: Maybe if you get a clarification of the question, of your patients, the patients which you see and treat, total patients, what percentage of your patients require the use and treatment of the two products that you use?

DR. ROSENBERG: A small number. I could get by with one of them.

At the meeting of the Alopecia Areata Foundation Medical Board, which was just the last week in March in New Orleans, I asked -- I told the group this meeting was upcoming and asked them just what their experience was with it and, first, everyone there uses this treatment. Everyone there uses this treatment, which is something to say.

The second was they felt it worked about half the time. Again, this is -- a lot of experience, though, in that room.

DR. RODRIGUEZ: I just have a simple question.

Since you have a foundation that you are associated with and you have just told us that at the meeting that people say -- 50 percent say it works, one of the questions that we are concerned about is safety. Most of these products have been used for over 20 years plus and even though anecdotally,

do we have any way of

-- I mean, that -- these people who are highly interested in the disease and who are supporting a foundation and associated, do we have any information that might assure us of, quote, unquote, the safety of this product? It might be anecdotal, but at least it is more than what we have on hand.

DR. ROSENBERG: I am unaware of any serious problems from it. I mean, the contact dermatitis, of course, but it goes away. Jim Davis, who wrote this thing, I said, how about the problems for the compounding pharmacist. So, he rolled up his sleeve. He said, well, here I have got a little redness here. He said I was mixing someone Tuesday and he said I am allergic to it and he said every once in awhile it will bother me a little bit, but it doesn't upset me.

So that I -- one would hate to, you know, bring historical evidence that it doesn't hurt patients, but I continue to -- I think it is safe. I certainly -- compared to the systemic corticosteroid, it is not a contest. It is safe. Compared to puva(?), where there elevations of soralin(?) UVA, of melanoma 15 years later, I think it is safer than puva.

Topical steroids don't work either.

DR. JUHL: Elizabeth, Larry and Bob.

DR. MC BURNEY: Dr. Rosenberg, I have two questions, one of which you have somewhat answered. Of the three agents,

which one do you think has been the most effective and is used the most frequently by dermatologists?

DR. ROSENBERG: I don't know that. To my knowledge, at least up to a few years ago, the Mayo Clinic was still running DNCB. They just never changed and then that was -- I was surprised when they told me that is what they were having. I think it was Sig Muller(?) was still there when they were doing that. But I didn't know anybody else was using DNCB anymore.

Do you?

DR. MC BURNEY: No. My impression is that it has fallen off since the other two -- in your practice, do you use primarily the squaric acid or the DPCP, would you say, equally or one over the other?

DR. ROSENBERG: Interchangeably. Mostly, I think, Hopley uses most mostly DPCP now. So, I use mostly DPCP now. He is very good. I am sorry he didn't come to this meeting. He is very, very good. He is very organized and does it in a very organized way.

DR. MC BURNEY: My second question is, and realizing this is anecdotal, just on -- but which I think is extremely valuable coming from someone like you who has treated many patients with alopecia areata, do you feel that of those two agents, the DPCP versus the squaric, do you feel of those two that one is more effective than the other?

DR. ROSENBERG: No. I think if this committee was more comfortable with the safety of one than the other and thought it would be useful to have one and just one, I could live with that, but there are patients who will become tolerant and no matter how strong you -- they say, well, it doesn't seem to make me pink anymore. Nothing happens.

Hopley has his patients come to the clinic once a week, where his -- actually, it used to be his wife painted it on when she was a nurse. My practice all along has been to write the prescription and teach the patient how to use it by -- we won't go into that -- dipping a cotton applicator into this acetone solution and waiting until it is dry and then touching it lightly and so forth for home treatment. So, both of those techniques are possible and patients will come in and say that it doesn't work anymore. They get a fresh bottle. Maybe it has gone off and they get a fresh bottle and that doesn't work and then so we will make it stronger and make it stronger and that doesn't work.

It is evident that they have become tolerant of the chemical. So, it is useful in those cases to have a second one. But that is not very common. That is rare in a rare disease with an unusual treatment. I think we could live with one.

MR. TRISSEL: A couple of points. One is I would suggest to your compounding pharmacist that he should wear

some protection, particularly gloves, just as a matter of common sense.

Let me ask the people from the Agency, is there any precedent -- are there precedents set for advocacy groups -- let me ask someone from the Agency, are there examples of interest groups or foundations holding INDs to evaluate some, say, orphan drug, for lack of a better term?

DR. DeLAP: Well, there are some products that have different than conventional approaches to IND process, I would say. Not every product that is under IND is being sponsored by a commercial organization that wants to market it eventually and, of course, a lot of them that aren't held by commercial organizations of that sort are held by individual investigators, but then there are still others that are held by organizations that are interested in having a particular product available.

We do have -- there is precedent for having INDs that aren't necessarily going to lead to a product in the marketplace, where really what it is is serving as a mechanism for having a product available to people in the U.S. for a disease that is perhaps so rare in the U.S. that there is never going to be a commercial development.

I think that the reason that people are interested in that or, you know, the value added, I guess, is the way I would express it for the Agency is that then we are looking at things like how is the product produced and manipulated

before it goes to the patient. So, we look at things like what is the source of the chemical? What is the purity? What are the impurities?

That is looked at under the IND process and there is at least some intent to learn as much as possible, understanding -- I certainly respect -- number one, I respect Dr. Rosenberg's experience. I also respect his -- it would be impossible to perhaps get a traditional gold standard kind of randomized control trial out there in this area. But, nonetheless, when we see these things under INDs, even if they are not headed in that direction, a lot of times there is an ability to collect some information that advances the state of the art over time, such that we can develop more experience to the best recipe, as it were, for using the product, the best way of -- you know, for compounding purposes, I mean, what is the best solvent and way of doing the compounding so we preserve the stability of the product and you get the least possible side effects from the patient.

You know, we can learn more about those kinds of things over time with the more organized research effort under an IND. So, you know, I think that that is very interesting concept and I would like to hear further as to what people think about that. I don't know if the academy would be interested in sponsoring that kind of an effort. It is not a trivial thing to do, but we always try and work with people

when we know that they are trying to do something like this for a special population of people that we need to be careful to serve.

We try and work with people that are interested in organizing these kinds of efforts to make sure it is not more onerous than it has to be.

DR. JUHL: Joan.

MS. LA FOLLETTE: Speaking of these other types of INDs that aren't from a commercial manufacturer or company, might be a private physician, I am not familiar with that type of IND, as far as what type of documentation goes in, but does that mechanism provide -- some of the concerns, where we are concerned about the source of the drug substance.

I mean, is that filed as I am going to use this supplier and then that is what it is limited to, such as the way a commercial IND would be.

DR. DeLAP: Yes, we do look at the source of the product and what is known about the purity and impurities and whether there are any issues that come to the fore from that. I think you got the sense from some of the presentations that our chemists made that there is a fair amount known about some of these products and there are different impurity profiles, some of which are probably better than others in some bulk products, we would rather people use if they are going to do this, and others, we would rather they stay away from perhaps

because of levels of carcinogenic impurities.

So, we do look at that and we do look at that and we do regulate that under an IND to ensure that we are getting an acceptable quality product.

MS. LA FOLLETTE: I had one more question for the speaker, the presenter. I understood in your talk, you were talking about Dr. Hopley and you said in Germany they had made some decisions based on positive Ames tests to ban -- this is what I understood you to say --

DR. ROSENBERG: That was my understanding, yes.

MS. LA FOLLETTE: Are some of these compounds available in Europe or are they also compounded?

DR. ROSENBERG: I think Hopley compounds it. He buys the chemical and compounds it. I don't think they are available as therapeutic agents, I mean, you know, from a pharmaceutical supplier, but I think they have passed -- my understanding was that the squaric acid and the DPCP had passed regulatory review there. They were two that he could use at that time.

MS. LA FOLLETTE: That may be interesting to this committee to know what source of drug substance and maybe there is a history of it being used in Europe. I mean, it just might be another avenue to collect more information since nobody enters into an IND here.

DR. ROSENBERG: It certainly is used in Europe.

Just without going over it again -- just what I hoped I was able to get across in three points. One is that alopecia areata is an important disease to people and one not to be dismissed just -- it is much more important than male pattern hair loss, in my opinion -- much, much more important than male pattern hair loss. I would not contribute to a male pattern hair loss foundation or serve on their board.

I voted against propecia when I was on the Dermatology Advisory Committee last year. It is an important serious disease for some people.

Two, I would submit that if you are not convinced it is effective treatment, that it -- we could put together a group of people who would come here, admittedly not with a gold standard peer review journal, double blind placebo, evidence-based, pass all the hoops of standards, but we could come in here with enough data to convince you that this stuff works, at least some of the time.

I have no question about that. I have no question that the committee would be satisfied and I would be -- if you wanted that, I am sure we could put it together.

The third is the safety. We are very grateful that this committee is considering the safety and it shouldn't be there unless you think it is safe. We appreciate the time and effort and thought that is going into this concern very much.

DR. JUHL: Thank you, Dr. Rosenberg. I think we will stipulate to points 1 and 2. Our question is how do we make this available for the benefit of patients in the safest way and at the same time begin to move the science a few inches forward.

The suggestion that I had made earlier that that would be a -- in my opinion, it would be an excellent venture for the academy to be the sponsor of an IND and collect patient information, not in the scale of a full-fledged trial that we would like to see if we had all the money in the world, because we don't, and a kind of a registry, maybe a registry of pharmacists.

Maybe after 20 years, we find all these people develop something and we have no way of knowing because there have been no records kept. It seems to me we could bring more order to the process, which should in the long run benefit patients.

Thank you, again.

DR. ROSENBERG: Thank you, sir.

DR. JUHL: We are seven minutes over our time budget. We will take a brief break and we will start the open public hearing at 10:45. So, please be prompt.

[Brief recess.]

DR. JUHL: Let us reconvene with a few helpful suggestions from our AD man. First of all, when handling

the mike, handle it from the base, not from the top. Please don't touch this, meaning the top of the microphone. And also make sure that you pull it so that it is as close to you as it is to me. If it is some distance away, he turns up the power so that you can be heard and that is where the feedback comes from. So, if we could follow good microphone etiquette, we will see if we can improve on the quality of the sound from here on in.

Agenda Item: Open Public Hearing

We now have the first of several open public hearing speakers that we will have during the next two days. During this session because we want to ensure fairness to all, we will have timed presentations. Our first guest is Larry Sassich from Public Citizen, who will make a presentation to the committee and he will have ten minutes.

Larry, welcome.

MR. SASSICH: Thank you very much.

I am Larry Sassich, a pharmacist with Public Citizen's Health Research Group in Washington, D.C.

Public Citizen strongly urges that the Food and Drug Administration's Pharmacy Compounding Advisory Committee consider the following four important issues: The nominated bulk drug substances appearing in the FDA's January 7th, 1999 proposed rules as substances that may be used in pharmacy compounding should be reviewed by appropriate agencies --

divisions in a manner similar to the drugs that will be discussed today and tomorrow and then be discussed by the Pharmacy Compounding Advisory Committee before this rule is finalized.

I would like to commend the Derm and Dental Products Advisory Committee on their rigorous review of what is known about these three sensitizers that was presented this morning. Even though some members of the committee might not feel that rigorous science is necessary, I think the public does and I think the reviews that were done this morning will make excellent newsletter articles for our consumer news letter that goes out to about 130,000 people.

My second point is five of the above mentioned 20 bulk drug substances are currently ingredients in commercially available products and, thus, should not be included on the list of substances that may be used in compounding. These are ferric sulfate, ferric sulfate hydrate -- and I think the FDA considers this as one compound -- phenindamine tartrate, phenyltoloxamine and taurine.

The third point, there should be clarification of the reasons for including currently marketed nutritional substances on the list. Three of the above mentioned substances are currently sold as nutritional supplements. These are choline bitartrate, glutamine and taurine. Taurine is also an ingredient in an FDA approved product as mentioned above.

Choline bitartrate is advertised heavily on the Internet as a brain stimulant. Glutamine as the -- will be the successor to creatine for body buildings and taurine, if I remember, is sold as to normalize the pH in the central nervous system. Ads for these products appeared on pharmacy Web sites on the Internet.

My last point and the most important, I think, is the use of abuse of pharmacy compounding. We feel that there is evidence for the abuse of pharmacy compounding. The nomination of DDMPS, a chelating agent, and piracetam, a brain booster, on the list of substances that may be used in pharmacy compounding are clear examples of this abuse.

The suspect use of DMPS is discussed in Public Citizen's comments submitted to the docket regarding the list of bulk drug substances that may be used in compounding. Examples of how piracetam is being promoted and what use it is being promoted and sold for are given below.

In considering the bulk drug substances that may be used in pharmacy compounding, it was the FDA's expectation that "fraudulent or quack remedies will be less likely to be included on the list because the practice of compounding such drugs is not expected to be sufficiently prevalent or longstanding."

Unfortunately, the misuse of pharmacy compounding for exploitation of the public may contribute to a significant

segment of pharmacy compounding.

There is a an unprincipled symbiotic relationship between some compounding pharmacists and exploitative practitioners of complementary/alternative medicine movement, each requiring and using the other for their own economic well-being.

The Web sites for the International Academy of Compounding Pharmacists and the Professional Compounding Centers of America link to the Web site of the American College for Advancement in Medicine or ACAM in Laguna Hills, California, an organization that claims on its Web site to be "dedicated to educating physicians on the latest findings and emerging procedures in complementary/alternative medicine, with special emphasis on preventive/nutritional medicine."

ACAM has been involved with the promotion of chelation therapy that involves the intravenous injection of EDTA, approved by the FDA for the treatment of heavy metal intoxication. We have been informed that an action is pending between ACAM and the FTC over charges that ACAM made unsubstantiated and false advertising claims that non-surgical EDTA chelation therapy is effective in treating atherosclerosis and that this has been proven by scientific studies.

Two weeks ago, the editor of Public Citizen's Health Letter, a newsletter for consumers, received a complementary

copy of the March/April 1999 issue of the International Journal of Pharmaceutical Compounding, a publication, as Dr. Loyd Allen mentioned -- he is the editor-in-chief of this particular publication and a member of this committee.

He was also listed as a consultant to Professional Compounding Centers of America in August in 1998, though, this announcement no longer appears on the PCCA Web site.

The International Journal of Pharmaceutical Compounding was delivered to our editor bundled with print and promotional materials from Smart Publications of Petaluma, California, an organization that proudly announces on its Web site, "We're the people who created the classic, international best seller, Smart Drugs & Nutrients, pioneering the concept of cognitive-enhancing substances.

A cover letter draws attention to an enclosed press release entitled "Natural Testosterone: Good for Your Heart." This is a chapter in a recently released book entitled Maximize Your Vitality and Potency: For Men Over 40, published by Smart Publications, a book that "covers natural testosterone and other supplements to reverse the effects of aging."

The cover letter goes on to say, "Also enclosed is a recent copy of the International Journal of Pharmaceutical Compounding in which the 'Heart Health' chapter is excerpted. What's the connection? Natural hormones must be custom prepared by compounding pharmacists because they are not

available from drug manufacturers."

The cover letter also invites our editor to "Please consider reviewing our new book or writing a story on these topics." The press release announcing the book says in part, and it is very similar to the above statement, "The key chapter on heart health from this book has been excerpted in the current issue of the International Journal of Pharmaceutical Compounding. What's the connection? Natural hormones, like natural testosterone, are available from compounding pharmacies represented by this journal."

At the end of the "Heart Health" chapter published in the journal is the following advertisement. Maximize Your Vitality and Potency can be purchased direct from Smart Publications. Wholesale pricing is available for pharmacies wishing to resell the book to customers (a good way to educate about the value of natural hormones.).

Also in the materials received by our editor was a newsletter entitled Smart Publications Update, apparently written for distribution to the general public. The newsletter advertises products, such as deprenyl citrate drops, piracetam liquid and triple natural estrogen cream as anti-aging products. On page 6 of this newsletter an article appears entitled "The Top Smart Drugs & Nutrients." Mentioned in this article is piracetam, a bulk drug substance nominated by compounding pharmacists. The article describes piracetam as "an

intelligence booster and CNS stimulant with no known toxicity or addictive properties. Piracetam has been described by many people as a drug that 'wakes up your brain.'"

Piracetam has never been approved for use in this country and there is no legitimate medical use for this drug that we could find.

In some Third World countries, it is promoted for the treatment of memory loss, in others for lack of concentration and in still others for intellectual deterioration. In India and Thailand, piracetam products are promoted for the treatment of mental retardation or learning problems in children. In Malaysia, Singapore, the Middle East, Mexico and Colombia, they are recommended for the treatment of alcoholism or alcohol addiction.

Two boxed advertisements appear on page 4 of the newsletter in close proximity to each other in the same style and with the same color highlighting. These ads are reproduced below without color.

Briefly, the first ad, "How to Find a Compounding Pharmacy." The easiest way to locate a compounding pharmacy is to contact the Professional Compounding Centers of American, Inc. or the International Academy of Compounding Pharmacists. They can be contacted as follows -- and their phone numbers are given and then parenthetically you can also ask these organizations for a referral to a physician near you.

The second adjacent ad is "How to Find a Knowledgeable and Understanding Physician." The quickest and most efficient way is to visit a medical doctor or osteopath, who is a member of the International College of Advanced Longevity Medicine or the American College for Advancement of Medicine. All members of these professional organizations are skilled and knowledgeable in the prescription and use of natural hormones and other alternative compounds.

These two advertisements show the completion of a treacherous triad between compounding pharmacists, complementary/alternative medicine practitioners and an unwitting public. Public Citizen strongly believes that the FDA and the members of the Pharmacy Compounding Advisory Committee must consider that some of the nominated bulk drug substances you will be discussing have no legitimate medical use and will be compounded by some pharmacists to exploit the public while making exploitation appear as a noble cause.

Thank you very much for your attention.

DR. JUHL: Thank you.

We will, of course, take your comments into the suggestion hopper for future meetings of this committee.

Agenda Item: Discussion and Vote on Dermatological Products

We now will move back to a discussion and vote on the product compounds that we have discussed in the morning.

Let me ask if there are general comments before I suggest a way of proceeding.

Carmen.

MR. CATIZONE: Mr. Chair, I have two points of clarification I had raised earlier. The first, I would ask representatives of the FDA to respond to, please. That is the question of if this committee recommends that a product not be included on the list of substances to be compounded and the FDA approves that recommendation, does that exclude that product entirely from practitioners and prescribers and patients or does it allow that product to be used to a more controlled system, such as the IND process?

DR. DeLAP: I think we are not interested in withholding products from people that may benefit from them. So, I would like to put that out first.

I think there are different mechanisms that people can access products. This is one mechanism we have discussed a little bit about the IND mechanism. And I think if there are products that people need to have access to, but it is your sense that you would like to see them accessed with a little more involvement of the FDA under the IND process, you certainly could give us that message.

I don't think you have to simply say "yes" or "no," this product should or should not be available because I don't think that is -- I don't see that as being what the discussion

is about today. I think really it is should it be available under this mechanism and if you feel strongly that it should be available, but you think we should work on perhaps a different mechanism, then that is a message you can give us, too.

MR. CATIZONE: Mr. Chair, with that answer then, a question to the committee in terms of what is our responsibility. If we agree and accept the fact that by not placing a substance on the list, that we are not excluding the availability of that product to physicians, prescribers and patients with a demonstrated need for that substance. It is not our responsibility, as somebody mentioned earlier to decide what the availability of those products should be, based upon the criteria, which the FDA has established.

So that if we place the substance on the list of substances that can be compounded, we are saying that that product is perfectly safe for any practitioners, duly licensed or registered to compound that product to use in any situation, including based upon information that was presented to us this morning to allow patients to home treat and titrate themselves with those medications or are we saying to ourselves we need to distinguish between products that are ultimately or perfectly safe and those products, which the FDA has produced data that indicate there is a concern and problem with safety and, therefore, we should allow those products to be available through a mechanism that addresses and manages those safety

issues so that the public and practitioners involved in the compounding of these substances are safe and protected from the concerns, which have been noted and published.

DR. JUHL: Well, with the exception of using the words "perfectly safe," which I don't think any -- is used any time at the FDA or elsewhere, I think that is the sense of the issue.

David.

DR. LIEBMAN: Piggybacking on Carmen's question, you have said that there is a mechanism whereby an IND can be obtained, give me a sense of the time frame. If I were to apply for an IND or if M.D. Anderson would apply for an IND today for one of these drugs, give me a time frame as to when they would have it such that it would be available and they could then dispense the product or the medication.

DR. DeLAP: Well, that is -- it varies to some degree, based on what the need appears to be in the particular situation. If it is a situation where there is an individual patient, who greatly needs to have a product and they need it today or tomorrow, then we do have mechanisms for that, for approving an IND and approving availability literally within a day in those situations.

The more standard approach is if we are getting a protocol in that deals with the treatment of potentially a large number of patients and it is a new IND, then under

our regulations, we have 30 days to review that and respond. Again, that is more for the situation where there is a research program that is being submitted with a protocol that we are reviewing and providing comments on. And, again, the timetable there is for us to respond within 30 days.

DR. LIEBMAN: Let me see if I heard you correctly then. If we were to put these on the non-acceptable list -- and Dr. McBurney has patients or Dr. Rosenberg has patients and they want to use either one or both of these drugs, they could put an application to your offices and within 30 days, they would have approval?

DR. DeLAP: Well, 30 days is the review time for an IND. The great majority of INDs are accepted within the first 30 day cycle. There are some that come in with some significant problems in the proposals that need to be worked through and there is a little back and forth that may take a little longer. But the great majority are finished within that first 30 day period and people can go ahead and start using the product and treating patients.

DR. LIEBMAN: One last question. Dr. McBurney has to put in an IND. Dr. Rosenberg has to put in an IND. Every physician who treats alopecia would then have to put in an IND if they wanted to continue using one or more of the products that we talked about this morning. I need a sense of clarification. I don't know the process.

DR. DeLAP: I think we would want to work with people to see if there was -- what was the most efficient way of dealing with this. If in fact there are a large number of individual physicians, who would want to be able to use these products under an IND mechanism, our preference would be to work with people to find some umbrella mechanism such that not each individual person would have to go through the IND process, but there would be some centralized mechanism such that people could participate in a consortium, as it were, and individually have access to the product without having to go through the IND process individually.

DR. LIEBMAN: One last question. For the two physicians involved, does that sound reasonable to you?

DR. MC BURNEY: I have a couple of questions just to follow up on what you said. If it is decided not to include it on the bulk list and that is upheld by the FDA, the decision of the committee here, then it is my understanding that immediately it will no longer be available to legally compound. Am I correct on that?

MS. AXELRAD: I would say once we -- once November 21st, 1999 comes, because we have this one year grace period, once we published the final rule and we pass that November 21st, 1999 date and assuming it is no longer under consideration, then strictly speaking it shouldn't be used for compounding.

DR. MC BURNEY: With that in mind then, all of the

patients who are using it or who potentially would be using it by then. For each patient we would have to submit an individual IND. Am I correct on that?

MS. AXELRAD: No.

DR. MC BURNEY: As a physician, if I am, say, treating 10 patients that way, what would be my recourse of action as a practitioner?

DR. DeLAP: I don't think we would envision people submitting INDs for individual patients. I think that we would envision people submitting INDs for their entire group of patients in their practice. Again, I would prefer that we could come to some way of having further organizations, such that people collaborate in this process and have mutually agreed upon programs, such that, in fact, we could have one IND that would cover multiple physicians and practices.

DR. MC BURNEY: My experience as an individual in practice, having applied for individual INDs for thalidomide before that was approved and so forth. We did it on an individual patient basis and the turnaround time I will say from the FDA was very prompt and they were very good about it and within 30 days I had my approval and so forth.

But even doing those, it takes about five hours of time to get everything together with the review -- you know, the hospital review board and everything else and to get the pharmacy and everything set up, the pharmaceutical

company. With these products, would we be held to a more intensive -- not having seen the forms that would have to be filled out, for, say, to treat ten patients with it, would it be a more extensive form? Are you going to, you know -- I am trying to get a feel for how complex it would be, I guess, is my question.

DR. DeLAP: Well, we have, really just one set of forms for INDs. You know, whether it is an individual patient or a group of patients or a major, you know, multi-center protocol, it is basically the same kind of paperwork involved in an IND process.

I think the thalidomide, of course, had some special issues and I think that we were trying to be attentive to some of the special concerns with thalidomide. So, you might have experienced a little more paperwork with that in some respects.

DR. MC BURNEY: So, actually, you would say that it would be less for -- if I wanted to do ten patients, I could do it as a group and not need individual patient data?

DR. DeLAP: That is my expectation. And, again, I think we have an interest here, too, that we don't want to go through a lot of paperwork from multiple investigators about a lot of individual patients. So, we really try and work with people to do this as efficiently as possible. Again, I think, thalidomide raised some special issues and we spent

a lot more resources internally on that and ended up collecting a lot more paperwork from people externally than we might have otherwise done.

DR. MC BURNEY: Can I ask you one other question? Would the FDA consider giving, say, a blanket one to something like the National Alopecia Areata Foundation and have physicians go through them in an approved source of getting the medicine if that organization was willing to oversee that.

DR. DeLAP: I think we would be comfortable with some kind of overarching organization like that, managing an IND if they want to take it on. I don't want to say that the paperwork is trivial because it is not. There is some paperwork involved, but it is a lot more efficient to have kind of an overarching organization with a lot of participating physicians than to have everyone going through it individually.

Obviously, we have a great vested interest in getting done what needs to get done, but getting it done with the least amount of paper that we have to look at, too. So, we are not interested in having things happen that would require more paper.

DR. JUHL: I think, unlike term papers, there is an advantage that the INDs all be the same. That has the opportunity to maximize the public benefit. I mean, that would be one of the purposes. So, it wouldn't be necessary or even desirable for individual physicians to ad hoc write

their own IND. It would be useful to use the same kind of information.

DR. ROSENBERG: Thank you for letting me come back, but someone asked a question. As someone who has written INDs, they are not trivial. That would be one thing. And as someone -- and when they get it, the Agency, they get a level of review, which is not superficial. So that my reaction would be to use the IND route as a means for us to continue what we are now doing, which is treating patients, because we think it is all right, would not be right. That is not what the INDs are for. It would be -- it is not fair to the IND process, which is much too important for that.

Very few physicians will fill these out. Those that do, they don't want to read them. I think individual physician's IND kind of behavior would be wrong on -- for several reasons. I haven't thought long enough. I am sure I could come up with more reasons but I think these are two good ones. I think it would be just not the -- INDs should be treated with more respect than that, both coming and going.

The second thing is, you know, what is an IND really trying to tell you. Is this drug safe and effective? And in terms of safety, how is it going to come up with safety? I mean, the doctor has no idea what company supplied the chemical. He doesn't know how it has been analyzed. He doesn't know anything. So, when the doctor writes an IND, we are

not going to know anything. If we wanted to talk about having an organization sponsor something, I think we could talk about it.

If we wanted to go back to the point I tried to make before was if we are talking about safety and efficacy, I think -- I did not prepare myself -- I must say, I did not understand the nature of this meeting precisely, that I would need to, you know, bring in all the efficacy data, as if I were bringing the drug before -- as a drug sponsor. I was speaking of the interest of the practicing physicians and I think did that fairly, but I think if you said let's have somebody who really wants to be a sponsor of this come in and present the case for it, I think the Alopecia Areata Foundation -- I can't speak for them, but I think it would be something they would certainly consider doing.

I believe with all my heart that this group or any other reasonable group would say the stuff seems safe enough and I think the people around this table and both the Agency and within the pharmacy review experts could tell us about the safety, in theory at least. In terms of experience with safety, I think there is no -- the whole question of Phase 4 study is, of course, an enormous one. Whether you would want a registry or not, I don't think so. I am repeating myself.

Thank you.

DR. JUHL: Loyd, other questions of clarification before we begin the discussion formally?

DR. ALLEN: Yes. For the presenters this morning, if the IND/NDA approach is used, the source of the product, as it is now for your standard INDs that comes from a manufacturer or single source, you know, maybe three lot, single source type product, if we look at a compounded product, would this be limited to coming from a single source, at which point it would then become a manufactured item or would it come from pharmacists throughout the U.S. that were participating in these studies? Would they be working from the same formulation or just how would this all work down at the bottom line level? Because we are almost moving it from a compound to a manufactured product.

DR. JUHL: Want me to offer an opinion on that? I believe the IND asks you to specify your method of manufacture, with a small "m." And I think to whatever level the group who was sponsoring or individual was sponsoring wanted to delineate that, it could be useful. And it may mean that they would say that the bulk compound should have a model certificate of analysis of whatever the most precise one is that we have and then that would allow multiple sources, as long as they met that standard with a similar certificate of analysis.

And then any pharmacist, who was operating under

that IND would be obligated to follow the manufacturing process that is specified, whatever it is. So, I think there is a great deal of flexibility in that, but it would allow the setting of standards and perhaps ameliorate some of the concerns that we have over the impurities and their possible contribution either to ineffectiveness or side effects.

DR. ALLEN: I was primarily referring to formulation instead of the source of the raw drug material.

DR. JUHL: And how it could be compounded could be specified.

DR. DeLAP: I think that is exactly how I would envision it. You would have some way of saying what your expectations are regarding the bulk substance and then you would also describe in the program what are the acceptable range of practices, as far as compounding it, to make the final product.

MR. TRISSEL: Yes. There are examples of products that have gone through the Agency that way. 2CDA, when we first had it at Anderson, we had to compound it under a set of instructions from a sponsor. But they had no product at that point. In fact, the first three or four batches had to be compounded before they finally had a product to test. That product, I believe, now is commercially on the market. So, there is an example of how it progressed. There is a mechanism for specifying or allowing compounding pharmacists

to do that through the Agency and the IND process.

One question I would like to ask about the three compounds that we have been discussing have been generally classed together, but one of our speakers, Dr. Rosenberg, seemed to make a differentiation between DNCB and the other two products. I was wondering if our other dermatologists would care to agree or disagree that there is a difference between DNCB and its safety and toxicity versus the other two in clinical use.

DR. MC BURNEY: I think what has happened is that when the Ames test data was made -- was widespread knowledge, was made available to everyone, everyone backed away from it clinically as a general group. As David has mentioned, there are people in his area that are still using it, but I think as a group they backed away from it and not because there was data about problems with its safety, but because of the fear that there could be potential danger and move to the other two products, either the squaric acid or the DPCP.

In more recent years, I think people are using more of that than the DNCB and that is -- I don't have any hard numbers on that, Larry, but that is just my impression in talking with people, who do this kind of therapy.

But there are still very good clinicians in medical centers, who are using DNCB, not frequently but for very

difficult cases.

DR. JUHL: David.

DR. LIEBMAN: I am sorry. As a practicing clinician who compounds, if an organization has an IND, clarify for me what that means to me at the compounding level. Can one of my physicians write for it because there is an IND somewhere out there? Do I need special permission to make it? Does he need to be a member of that association? Do I need to get it from a particular source? Lots of questions. And I need to know what that means to me as a practitioner.

There is one thing -- let me just say when M.D. Anderson is doing it, it is all in one building. That is kind of easier. If you have got 50 or a hundred or 200 or 500 pharmacists around the country, who are going to be impacted by it, but individually, give me a sense of how we are going to be impacted, what this means to me at the patient level.

DR. JOHNSON: Well, both of these, both the physician and the pharmacist need to be tied to the IND in some way.

DR. LIEBMAN: Does that not create an automatic nightmare? Do you send a list around and say how many compounding pharmacists in the country would like to be tied and if I want to be tied, if I don't want to be tied now and a year from now, one of my docs says, David, can you do so and so, where does that place me?

DR. JUHL: I think the tie goes through the

physician.

DR. LIEBMAN: Does the physician have to be a member of the National Association of Alopecia Treaters, blah, blah, blah? I hear lots of -- I don't mean to be a pain. Okay? I am a practitioner. I need to know exactly what this means to me, to my doctors and to my patients and I need for you all to understand clearly that whatever -- you know, in your wisdom you decide this is the best way to go, that is fine and I will have to live with it, but I need to know that you know that when you vote for something or when you agree to something, these are the ramifications and I am at the patient level. I am at the doctor level. I am at the patient level. I am at the compounding level. So, I am going to be impacted very clearly by whatever decisions the committee makes, whatever recommendations you do to the FDA.

DR. DeLAP: I think the way it is usually done would be to have a list of the participating physicians on the IND and then those would be the people that are empowered to write the prescriptions and add the patients to the program. I am not sure -- you were describing your M.D. Anderson experience. I mean, ordinarily, I think, the people that the physician works with professionally don't really need to be specified to the level of detail, as long as you have someone that is identified as being the responsible person at that site.

Again, often times it is just the physician who

is actually writing the prescription and administering the treatment. So, we don't ask for information on who all might be involved in preparing the product for the administration, for example.

DR. JUHL: The only responsibility would be to the pharmacist, who was preparing it, would follow it according to the manufacturing process.

DR. DeLAP: We would expect people would be appropriately licensed and follow their usual, you know, good practices, but we don't ask for that kind of information ordinarily.

MR. LIEBMAN: My last comment and I will let you go. If the Alopecia Society does this, what does that do to Dr. Buddy Cohen at Johns Hopkins, if he is not a member? Ergo, he can't participate? If I don't get asked, do I want to be one of the participating pharmacists? A year from now, what happens?

What I am hearing is you are about to create a nightmare. If you want to go with saying, oh, we will vote it off the list but we will do an IND, when you start looking at the mechanics of it, it is a monstrosity. I think the voters need to think about that. It is one thing to do it in an enclosed institution. There is something very different about doing it to a physician group nationwide and a pharmacist -- 50,000 pharmacists, pharmacies nationwide.

I envision lots of problems.

DR. DeLAP: I think there are definitely tradeoffs and I think you have eliminated some of the issues very clearly. I don't think anyone would have a monopoly on this kind of thing. I mean, if there was an AA sponsored program that served as an umbrella for many physicians across the country to do this with minimal personal paperwork, that wouldn't mean that someone at Johns Hopkins couldn't say, well, I want to be on this and then if for whatever reason they couldn't just get added to the AA sponsored program, they could -- you know, they could file their own protocol and do it if they wanted to.

So, there is no law that says that if there is one umbrella organization that is doing it that nobody else can. I agree with you that there are some very real logistic questions that come up and I think I would say that it is not our interest anymore than it is yours to have it be onerous or impractical. We do have to do the best we can to manage those issues. There is a little time, as Jane was saying before this actually takes effect anyway, but not a lot and we have to do the best we can to get things organized so that it wouldn't be -- wouldn't disrupt people's lives too much.

The only other thing I would add is, obviously, the compounding list is a living document. It is not set in stone and if it was decided later on that the public health

advantage was to just put one or two of these compounds on, even if they hadn't been put on originally because it was just not working otherwise, you know, we could always revisit the issue, too.

MR. TRISSEL: To address your concern at many sites, it was M.D. Anderson, but it was also a number of other hospitals that were participating in this early phase study of 2CDA. So, we had different pharmacies and different physicians from different institutions all listed on the same IND. The pharmacies were not cited by individuals. The IND just said that the product would be made according to the set of instructions in the institutional pharmacy. That is about as far as it went. To add physicians was a matter of adding a name to a list, along with their C.V. to show appropriate credentials, if you want to add an investigator to that list.

DR. LIEBMAN: That is easy to do at an institution. Independently, it is hard. I know you don't mean to make it difficult and I know you are not trying to exclude anybody and I know that we don't set it up in terms of, well, we can do it but nobody else can do it and we are going to exclude everybody else, so our members have control over it.

Forgive me. It gets worse and worse as I listen. It just gets more and more difficult, more and more complicated and the ones who are going to suffer are the patients. That is my real concern is patients are not going to be able to

get what they need and physicians are not going to be able to treat their patients.

DR. JUHL: Who are prescribers in your experience for this? Are they primarily dermatologists? I would expect so.

DR. LIEBMAN: They are all dermatologists. One is a dermatologist, who teaches at Johns Hopkins in the medical school. Another one is a community dermatologist, who teaches at the University of Maryland. There are other practitioners, who have --

DR. JUHL: I think there is no denying that it will offer an extra level of bureaucracy, but I think you are going far off the edge of the fence on how bad it is going to be.

DR. LIEBMAN: I would love to be wrong on that issue.

DR. JUHL: Let's assume that it is dermatologists and they need to be part of this process. It would be a simple matter, as Larry said, of them submitting their C.V. to whatever organization this is and being listed on the IND. That would take care of the physician. From your perspective, all you would need to know is that the physician is on the IND and what the protocol for preparation is. I can see that being widely distributed to all compounding pharmacists all over the country.

DR. LIEBMAN: And to all dermatologists across the country to let them know that if they choose to use this,

they need to have their name -- because I think if we do that, that needs to be a condition.

DR. JOHNSON: Well, absolutely, absolutely.

DR. LIEBMAN: Okay. If you can work it out, I think it is great. You know, I am not opposed to it, but I think we need to anticipate what are the potential problems and try and figure out how to solve them before it goes into effect. That is all. That is my concern.

DR. JUHL: I agree.

Let me suggest a little -- a path for us to take here. A little bit ago, when Dr. Rosenberg was up, I spoke for the committee and stipulated that I think the committee probably believes that these compounds are useful in some patients some of the time. I want to make sure that I wasn't stepping across the boundary. Is that a reasonable -- can be -- does anybody object to that, I guess?

Well, let's make that assumption that that is the case and you will all just have to stop me when I get too far down the road here. And, again, looking at the drugs as a class and we do need to do some individual things, but as a class, we also see if we examine our four criteria of chemistry, historical use, safety and what is in the literature, that there is some difficulties in chemistry.

One of the foundations, the bedrock of drug development is to get a drug that you know what it is. You

know exactly what it is. You know its impurities if there are any and you use that all throughout to do your clinical trials so that you can relate back to -- this is actually what happened and how and why it happened. We don't have that with these compounds in that there is variability in what comes down the pike and in some instances we may not be concerned about that, but with these drugs, I think we may be because the impurities may be carcinogenic or have other problems.

So, there is -- in my mind, some chemistry problems. I am satisfied with the thorough work that the Agency has done. Does that reflect the view of the committee at this point?

Loyd.

DR. ALLEN: Yes. I will just go ahead and add that if you recall the USP has stated that they will go into the adoption of any standards that might be required for these. You know, and also keeping in mind that there is a number of products that we have currently in use, that we don't have the full information on. So, these four here may be -- the three here may be just a little bit different. But as far as the standard setting, I don't see that that could not be done within a reasonable, you know, length of time.

Then to our issues of safety, I think there is particular concern here about not only the safety of the patients,

but also health care workers. This seems to be in my mind a bit special compared to other products that we have worked on.

I think then the issue before us is whether or not we would like to recommend that these products be listed or not and if we recommend that they not be listed, is the attraction of the IND route one that could be turned into reality without creating a nightmare for patients, as well as practitioners, keeping in mind that the FDA cannot force someone, any group, to submit an IND. They can use friendly cooperation and persuasion, but the Agency isn't in a position to be able to mandate this happens. So, we would be -- if we were going to recommend that they not be listed with the hopes that an organization come forward to develop the INDs, we would be taking a little bit of an act of -- a leap of faith to assume that that would occur.

Now, having gotten to that point, are there differentiations that you want to make between the compounds before we actually take a vote on them? DNCB seems to have fallen by the wayside because of some of its special toxicity situations, although it is still being used.

The question I have, do we want to lump them as three and act on them in general or do we want to do them one by one? I am seeing heads shake "no" about doing them as a lump and to do them one by one. Is that -- head shakes

don't do well on the transcript.

DR. MC BURNEY: I would request that we do them one by one.

DR. JUHL: Okay. Then, in turn, let's start with DNCB and dare there any additional items of discussion on that?

Are you ready for the question? My assumption is that the question is to recommend that it be listed or recommend that it not be listed with the hopes that an IND process can be worked out. Is that the question you want answered? Okay.

Let's have a call for the question. Those who are voting members, let me remind myself that David is an industry representative and Joan is an industry representative and the rest are voting members up through Loyd.

Call for the question. Those that favor list -- recommendation to list DNCB, please raise your hands.

Seeing none, those that to not list DNCB, please raise your hands. I see that as a unanimous recommendation from the group to not list the compound.

Moving to our next alphabet soup, DPCP, let's follow the same process. Discussion?

DR. MC BURNEY: I cannot speak for the American Academy of Dermatology. I am only sitting here as a member of the committee, but I can give some opinions about what their approach would be having sat on their board of directors.

The American Academy of Dermatology is an educational organization and that is what is so stated in its mission statement. There is no organizational structure nor fiscal notes available to support a study that we are proposing. Ideally, it would be a very good place to have it and certainly we could approach the executive committee of the American Academy of Dermatology, but I doubt that that would receive a very high priority. I could be wrong on that. We certainly would need to look at it, but I think on the list of projects before them, that would not be put very high for the reason that it would not affect the majority of its members, would look at it that way.

And that there are more pressing issues, such as skin cancer that they would -- there is a greater number of patients that we treat with that disorder that they would want to put their dollars toward. So, I don't think it is realistic to look to the American Academy of Dermatology. If we did look to the National Alopecia Areata Foundation, certainly that would be very nice for our patients with alopecia areata, but what about all our other patients with warts?

We would then have to look at other individual physicians or institutions. There is no National Wart Society. There should be because there are a lot more warts than there are alopecia areata, but there is not. So, we have got --

we still haven't addressed all those other patients that it is being used for.

As I said, this is only my personal opinion on that.

DR. JUHL: Let me ask you, are the majority of practitioners, who would use these products to treat warts the same people who would probably be using the products to treat alopecia? Are they primarily dermatologists?

DR. MC BURNEY: They would all be dermatologists, I think, generally. Now, some of the warts, they may -- I think the other groups we would need to include, of course, would be our family practitioners who would probably perhaps use some of this. There might be some internal medicine people who would use it.

I cannot speak for pediatricians. I do not know any pediatricians and I couldn't speak to infectious disease. The buck stops with the dermatologists, I think.

DR. JUHL: For the record, Dr. Rodriguez said he would refer those patients to a dermatologist.

Let me ask the question of the Agency. It would seem to be some extra work but not much for an IND to include both. Could the same mechanism be used -- the same IND be used?

DR. DeLAP: Certainly in principle. I mean, we do have INDs that cover multiple indications and don't require additional -- you know, another IND and another set of paper

work. Again, I would like to stress that our interest in this is really not to deny this approach to anybody that really looks like they need to have it. Our interest really is just to do what we can to address some of these -- the chemistry concerns and the safety concerns and to learn a little more about the products as time goes on.

So, that is really where we are coming from and we don't want to limit the ability of somebody who really needs these kinds of treatments to get it. And we are very concerned -- again, I come back -- we are very concerned about logistical issues and we will look at these issues as carefully as we can and try and minimize them to the best of our ability. Again, we can -- I would say, again, we can revisit this whole subject if it turns out that logistically that it is too much of a problem to do it the way that we start.

MR. CATIZONE: Mr. Chair, I think there are two issues here and I would ask for some assistance with trying to understand how we differentiate or complement the two. One would be the question of safety. If this committee has a concern with the safety of a product and not addressing that safety by placing that substance on the list means that it is free for use for everyone, every practitioner duly licensed or registered to do so, including patients to self-medicate or self-treat, versus the issues raised by David and Elizabeth, which is access to those medications, can't our recommendation

be that if we have those safety concerns, we separate that issue and recommend that those products not be included on the list, with the proviso that these medications be made available through the IND process or through working with the Agency.

If that doesn't occur, if we receive information that the process is too burdensome or patients are being denied access, could we revisit the topic and then place those medications or those substances back on the list?

DR. JUHL: I think that is what was suggested. I think that is reasonable.

MS. AXELRAD: Can I make one comment?

With regard to self-medicating and taking it home, I would remind you that we propose to limit the use of some of the other products that we addressed at the last meeting for office use only. So, we think that that is an option and that would address some of the safety concerns.

DR. JUHL: Other comments on DPCP? Are you ready for the question? Same question?

DR. MC BURNEY: Can I make an amendment to the -- can I make one of them be that we would include -- if we are going to talk about DPCP -- be administered in a physician's office and be put on the bulk list, as we did with cantharidin. Can that be one of those?

DR. JUHL: We could, indeed. The question that

we will answer is, number one, to recommend that DPCP be added to the bulks list with the restriction that it be limited to application in the physician's office or, secondly, we could recommend that DPCP not be added to the bulks list with the expectation that if there is sufficient interest, that the Agency would work with a willing group to go the IND route.

Clear on the question?

All those who would favor recommending DPCP be added to the list with restrictions, please raise your hand. We have five voting for that option.

Secondly, those that would recommend that it not be added to the list, please raise your hand. We have five with that option. The chair breaks the tie by siding with the second option of "nay." So, it is 6 to 5 for option 2.

Let us move then to squaric acid dibutyl ester. Is there anything that we haven't covered in the first two that you would like to cover with this one or any difference in the chemical itself that we should consider?

Bill.

DR. RODRIGUEZ: I want to raise a question. Assuming that IND doesn't go through, how long would it be before we get the screamings, for example, to let us know that the system isn't working? In other words, I am just sitting over here, again, as somebody who has no direct effect in terms of my patients, but on the other hand, I am just

thinking over here, saying, gee, how long is it going to take before we know that 50, 60, a hundred, 250, for example, and what the mechanism is going to be.

DR. JUHL: I think we have between now and November 21st to get an indication that the process is not only possible, but it is something that can be workable and the Agency has expressed their concern that they want to make sure that this happens in an appropriate way. So, I think between now and then, we would be able to tell that the process could work were the situation such that -- it is not going to get completely done by then. There would be ways to make sure that it happens in a way that it doesn't disadvantage people. I don't want to speak for the Agency, but that is what I thought I heard you say.

DR. DeLAP: I think, again, our primary goal here is that the patients get the best possible advantage out of this. I mean, the best possible advantage for me is that they have access to the product and they have access to it in a good form. It is a good chemical. It is well-formulated. It is well-administered and that they get the best possible results as a result and that we learn more about it along the way.

I don't think it is a black and white situation in the sense that things will -- you know, that November will come and it will be absolutely a total flop or that it will

be totally working. I think we will probably be somewhere in between, but we will have to look and see how much of a burden it appears to be placing and if there are limitations on access, we have to look at that very seriously. It is not -- I am sure it is not going to be perfect going in, but we will do our best to make it as good as possible and, again, we can always come back here for discussion if it seems to be just too far out.

DR. JUHL: I believe the committee's next meeting will be in the fall, prior to the November 21st deadline, and, obviously, we would be interested in a report back on that as to whether or not --

DR. LIEBMAN: Point of information.

DR. JUHL: -- we should reconsider the issue.

DR. LIEBMAN: If between now and the fall meeting, someone tries to get an IND and there is a problem, could we possibly look at these drugs again since we now know that the -- if we find that the IND mechanism is not going to make them available?

DR. JUHL: Yes. I think that is what I said. Yes.

Elizabeth.

DR. MC BURNEY: I am sorry to be so persistent, but I just want to be sure we haven't -- I don't want us to blind ourselves that there is not another option, another way of doing it so our patients can still have the medicine.

Is it possible since what I am hearing from our distinguished people at the FDA, who have spent a considerable amount of time looking into the safety data -- and I have great respect for that -- is it not possible to somehow limit it to a mono source for the next drug we are going to look at so that what is available for bulk compounding comes from only one source? Is that possible? So that we could say not only does it have to be done only in a physician's office, but only from one -- we will allow bulk from one area, from one source.

MS. AXELRAD: I am hardly the expert on this, but I would say that it could possibly come from multiple sources, but we would look at the source and we would -- I mean, the way we usually do it for an IND is that they provide information on what the source of the drug is and the method of synthesis and the impurity profiles and we would look at that. If someone wanted to propose two sources or three sources, that would be all right.

We would still be able to look at that and make sure that it was acceptable. We wouldn't want to say it has to be only one source. It might be perfectly fine for it to come from two or three different sources, as long as it is produced in a way that provides a quality product.

DR. DeLAP: I think you are talking about under IND, though.

DR. MC BURNEY: Yes. I was talking about under bulk.

DR. DeLAP: She was asking about under bulk, compounding, whether we could specify a limited number of sources where it was acceptable for compounding purposes.

MS. AXELRAD: No. I am sorry. I misunderstood the question. Compounding, as long as it is a registered manufacturer and it is provided with a certificate of analysis, that is what the statute requires.

DR. JUHL: Other questions?

We shall then move to squaric acid with the same question. We will use the same options. Option No. 1 is to recommend that squaric acid be listed on the bulks list with the restriction that it be used only in the physician's office. Option No. 2 is that squaric acid not be recommended for the bulks list.

All those that favor recommending listing, please raise your hand. We have six.

All those who favor Option 2 of recommending not to list the drug, please raise your hand. Four and the chair votes "no." Five. So, it is 6 to 5 in the other direction, squaric acid being recommended to be listed.

Any final comments?

[There was no response.]

I would like to add my thanks to the Agency for

all the reviews that were received. It has been a tremendous amount of work on your part and it has required work across the disciplinary lines within the Agency and I know that doesn't always work smoothly. It certainly doesn't at my university. It requires some extra effort, things that you probably didn't plan on doing. So, I really appreciate the effort that it took to put that together.

We will adjourn for lunch and reconvene at 5 minutes to 1:00.

[Whereupon, at 11:55 a.m., the meeting was recessed, to reconvene at 1:00 p.m., the same day, Thursday, May 6, 1999.]

A F T E R N O O N S E S S I O N [1:02 p.m.]

DR. JUHL: We will reconvene. The group will now make a flawless transition from dermatology to neurology. We have a number of new people from the Agency at the table and I would ask you to introduce yourself in the microphone.

DR. BEHRMAN: Rachel Behrman, deputy director, Office of Drug Evaluation 1.

DR. KATZ: Russ Katz, acting director, Division of Neuropharmacological Drug Products.

DR. FEENEY: John Feeney, medical officer, Division of Neuropharmacological Drug Products.

DR. SOSTEK: Andrew Sostek, clinical reviewer, Neuropharmacology.

DR. JUHL: We have a series of presentations this afternoon on 4-aminopyridine and 3,4-diaminopyridine. These are drugs that are used to treat very serious conditions for which there are few options. At present, these drugs are not of the USP monograph or an NDA'd product and they are made available to patients sometimes through pharmacy compounding and sometimes through the IND route.

We will be reviewing a number of issues regarding these drugs and Dr. Feeney will begin the presentation. I will turn it over to you.

Agenda Item: 4-aminopyridine

DR. FEENEY: Thank you.

My purpose is to give a brief overview of the aminopyridines. Additionally, we have various specialists here today, who will also speak to their personal experience with the use of the aminopyridines, both 4-aminopyridine and diaminopyridine.

Dr. Sanders from Duke will later talk about the use of diaminopyridine in a rare disorder, -Eaton Syndrome and Dr. Bever from the University of Maryland will hopefully share his experience with the treatment of MS patients with both 4-aminopyridine and diaminopyridine. Then we also have three commercial sponsors, who will talk to you.

Again, my purpose is to provide a brief overview of both drugs, first for 4-aminopyridine . 4-aminopyridine is a potassium channel blocker that can be used to enhance the propagation of action potentials along injured axons and to enhance synaptic transmission. It has been used in patients with MS to improve neurologic function, as well as patients with chronic spinal cord injury.

4-aminopyridine is commercially available as a white to off-white crystalline powder. It is unstable at room temperature if exposed to light and humidity. Special care may be needed for handling bulk material because of potential toxicity if inhaled, absorbed through the skin or swallowed.

There are two reasonably sized controlled trials of 4-aminopyridine in the treatment of MS mentioned in the

literature. This first one is published in detail, while details of the second study are not completely available. In this first study published in 1992, 70 MS patients with chronic stable deficits were treated for 12 weeks with 4-aminopyridine or placebo and then crossed over to the other treatment.

At the end of the study, there was a small but statistically significant benefit seen on the expanded disability status scale, a standard 10 point rating scale in MS studies. Also, while 10 4-aminopyridine patients improved by one full point on the EDSS, no placebo patients did so.

This one point change is generally considered to be clinically meaningful. The dose used in this study was 0.5 milligrams per kilogram per day, which for an average adult would be about 35 milligrams per day. We know that during the open label extension study, two of these patients went on to have convulsions.

A second larger study was performed, presumably following up on the positive results already seen. This second study enrolled 161 MS patients in a six week parallel trial. No difference was seen in the number of patients improving on the EDSS at the end of the study.

Approximately 20 percent of patients improved in both treatment arms. The dose that was used here was 45

milligrams per day of a slow release formulation. Several seizures were also seen in this study.

Now, chronic spinal cord injury can be in many ways analogous to stable MS and 4-aminopyridine has been used in spinal cord injury patients also. While this 26 patient crossover study found no difference on its specified primary outcome, a composite endpoint, there were trends in favor of the drug seen on a sensory scale, as well as a patient global assessment scale.

The dose that was used here was 35 milligrams per day, again, of the slow release formulation. Later today, hopefully, Dr. Ron Cohen can talk about a larger, 60 patient study that was performed also in spinal cord injury. Those results are not yet published in the literature.

Here you see the common adverse events that are seen with 4-aminopyridine and I think the same profile exists for diaminopyridine, although with diaminopyridine, you may see more of the abdominal pain and paresthesias predominating. But the two more serious concerns are listed here. One is a realized problem and one is a possible problem that really merits further evaluation before we can say much about it.

Seizures are the major concern with the use of 4-aminopyridine. In our literature search, we found a total exposure across all diagnostic categories of 409 individuals. That would include patients with spinal cord injury, MS,

botulism, anything. The individuals were treated with different doses, ranging from 15 to a hundred milligrams per day. Likewise, they were treated with different formulations, varying from immediate release to slow release and peak blood levels would be expected to be lower with the slow release preparations.

But ignoring all those differences, we found six seizures for an overall risk of 1 in 68 for a risk of convulsions.

The QT interval on the electrocardiogram is directly related to potassium currents in the heart. It is strongly predicted that a potassium channel blocker, like 4-aminopyridine or diaminopyridine, would prolong the QT interval and put patients at risk for cardiac arrhythmias that could in some cases lead to sudden death.

While QT interval prolongation has not been reported with 4-aminopyridine or diaminopyridine, we are not sure that it has been adequately assessed in the experience to date. There are two reports that raise concern. Both are with diaminopyridine. The first is the report of a death attributed to MI in a middle-aged patient, newly exposed to diaminopyridine for -Eaton Syndrome.

Unfortunately, the details of that case are unavailable. The second case is that of an older woman with an inadvertent overdose of diaminopyridine. Initially, she

had convulsions, but four days later, as she was recovering, she had an unexplained cardiac arrest. Fortunately, she was resuscitated and survived without sequelae.

Diaminopyridine is also a potassium channel blocker that can be used to enhance the propagation of action potentials along injured axons and to enhance synaptic transmission. It has been used in patients with MS to improve function, but its main use has been in the treatment of -Eaton Syndrome.

-Eaton is a rare disease, which can occur either spontaneously or in the setting of cancer, especially lung cancer. Antibodies are produced, which affect the calcium channels on presynaptic neurons. Synaptic transmission is reduced and patients experience muscle weakness and autonomic symptoms. Perhaps only 300 patients are affected in the United States at any given time.

Diaminopyridine is also commercially available as a white crystalline powder. Like 4-aminopyridine, it is also unstable at room temperature if exposed to light and humidity. In 1989, McEvoy, et al., published this report in The New England Journal. The authors enrolled 12 patients with -Eaton in a crossover trial with three day treatment periods. Not only did symptoms improve, but there was good electrophysiologic correlation with the doubling of compound muscle action potentials.

The dose that they used was a hundred milligrams

per day. One of their 12 patients had a convulsion after ten months, but was able to continue successfully on a lower dose of the medication.

Donald Sanders, who is here today, recently reported on his ten year experience at Duke University treating Lambert-Eaton patients with diaminopyridine. Roughly half of his 40 patients returned to normal levels of functioning. In his report, Dr. Sanders mentioned an ongoing trial, which, hopefully, we will hear about more today.

Diaminopyridine, like 4-aminopyridine, has been studied in MS patients. Dr. Bever performed a 36 patient crossover study. Treatment periods were 30 days long, with a 30 day washout period. The dose used was a hundred milligrams per day. Favorable results on measures of leg strength were seen in the trial.

Paresthesias and abdominal pain, limited dosing in seven patients and one convulsion was recorded. So diaminopyridine, we have the same two safety concerns that were discussed for 4-aminopyridine; namely convulsions and QT prolongation. For diaminopyridine, we had a total exposure in the literature of 300 individuals.

Ignoring one convulsion that was in a patient with brain cancer and a convulsion attributed to theophylline toxicity, we found three other convulsions, which would leave a risk of about 1 in a hundred for convulsions.

It is because of the risk of convulsions and our concern about QT prolongation with both of the aminopyridines that the Division of Neuropharmacologic Drug Products believes these drugs should not be put on the compounding list at this time.

We believe that current experience with both of the drugs should allow for the accumulation of more data to hopefully improve their later safe use. And as the afternoon goes on, alternative distribution mechanisms that have been proposed will be discussed in more detail.

Thank you.

DR. JUHL: Thank you.

Are there questions on the presentation -- and, I guess, before I get to that, let me welcome Dr. Sid Gilman to the table. Dr. Gilman is the chairman of neurology at the University of Michigan and chair of the FDA Advisory Committee on the same topic.

Welcome, Sid.

Questions for Dr. Feeney?

MS. HOPE: I have one question. Do I understand correctly that there are two of these studies that use this slow release form?

DR. FEENEY: No, I am sure there -- I know there are more smaller studies that have used the slow release form.

MS. HOPE: And this was a commercially available

slow release form so that I guess my relation to this is that if this were to go on this list, that then compounding pharmacies would not necessarily be compounding a slow release formulation that was comparable.

DR. FEENEY: That is correct. I would guess that most of the compounded product would be immediate release and Dr. Bever has studied the relationship between C-Max and convulsions. He may talk about that today. He believes that there is a relationship between the two and with the slow release formulation, there may actually be a lower C-Max and less of a risk.

DR. JUHL: Other questions of clarification?

[There was no response.]

Thank you. I am sure we will be calling on you again later.

Next is Dr. Chris Bever of the University of Maryland, professor of neurology.

DR. BEVER: Good afternoon. I have been asked by the staff to discuss our experience working with 4-aminopyridine.

DR. JUHL: By the way, those slides were handed out at lunch to the committee members. There should be a piece of paper that the first slide has Dr. Bever's name on it.

DR. BEVER: And it is my responsibility that they

didn't get to you until lunch. So, I apologize for your not having more time to go over them.

I thought I should review just briefly some things about multiple sclerosis. I wasn't sure how much all the members of the panel knew about it.

There are about 250 to 350 thousand cases of multiple sclerosis in the United States. It is a disease that has its peak age of onset in the twenties and thirties. It generally does not significantly reduce life expectancy. So, it is a significant cause of neurologic disability, beginning in young adulthood.

It is a chronic inflammatory, demyelinating disease of the central nervous system. It can follow either a relapsing remitting or a slowly progressive course and it produces a wide range of neurologic symptoms, which relate to the location of lesions within the central nervous system.

Okay. There are treatments for multiple sclerosis and there has been quite a lot of interest in those treatments, but the newest treatments on the market, I would like to point out are preventative treatments, not restorative treatments. So, they do not offer symptomatic relief to patients with deficits from multiple sclerosis.

There are no treatments for some of the most common and disabling symptoms of multiple sclerosis, such as weakness and many patients have multiple symptoms and the available

symptomatic treatments are generally effective only on one symptom.

The pathology of multiple sclerosis is one of inflammation with demyelination and accidental loss. Conductional abnormalities are produced by demyelination with swelling of action, potential propagation and blockade of actual potentials in some situations.

There is evidence that some deficits in MS patients are physiologic; that is, not anatomic loss, but physiologic derangement of nerve functioning. That comes primarily from studies of the effect of cooling and warming MS patients; that is, symptoms in some patients improve with cooling and they worsen when patients' core temperatures are elevated.

There are two mechanisms related to demyelination that are proposed for 4-aminopyridine in MS patients. The first is improving action potential duration amplitudes and velocities in demyelinated axons and the second is to increase transmitter release with reduced numbers of axons and synaptic endings.

There were a number of early studies of 4-aminopyridine in multiple sclerosis. The initial was an open label study that was done in the U.K. Then there were a series of partially controlled and partially blinded studies that were carried out by Floyd Davis and Dusan(?) Stephaski(?), at Rush Presbyterial Hospital in Chicago. In these studies,

improvement was seen in a variety of deficits in MS patients. It did seem to vary from patient to patient. The side effects were relatively minor in a total of about 59 patients who were treated in these studies and the exposures were up to about one week.

The only side effects that were reported were paresthesias and dizziness. No serious adverse events.

That work led to the study, which has already been mentioned this morning by Chris Pulman and others in Amsterdam, which was a randomized, double blind, placebo controlled crossover design study, included 68 patients, who were treated for three months, no serious adverse events were reported in a 204 patient month exposure period and there was, as mentioned before, an improvement in overall disability scores in those patients.

This summarizes the side effects from those patients with dizziness being by far the most common paresthesias, fairly common gate problems, abdominal pain and anxiety, less commonly.

Responders from that trial were put into an open labeled safety study. There were 23 patients who went into that trial. Treatment durations were from 6 to 30 months. Most of the patients reported sustained improvement during that time. Two patients, as mentioned before, had grand mal tonicoclonic seizures. One patient was reported to have had

a chemical hepatitis.

We were then approached by Elan Pharmaceutical Research Company to do a study, looking at pharmacokinetics and efficacy of 4-aminopyridine. This was looking at an immediate release formulation. We did a randomized, double blind, placebo controlled, concentration controlled, crossover over design trial in eight patients who were treated for up to 36 hours.

This study, again, was mentioned earlier in that we saw there was a relationship primarily between the area under the curve or total drug exposure and improvement of neurologic deficits. We also saw a single seizure in the patients whose drug levels were being monitored at the time of the seizure. So, we knew that the level was about 104 nanograms per ml. In general, in looking through the occurrence of adverse events and looking at the actual serum levels in those patients, there appeared to be a reasonable correlation between symptoms and peak levels.

DR. JUHL: Could I ask for a clarification on that point?

DR. BEVER: Yes.

DR. JUHL: The people who experience seizures had high peak levels or the seizures occurred at the time you would expect --

DR. BEVER: The seizure occurred at the peak and

a number of other side effects also occurred coincident with the peak or close to.

This formulation was then tested in an efficacy study that was carried out at the University of Rochester. It was a randomized, double blind, placebo controlled, crossover trial. Ten patients were treated for up to seven days with a slow release formulation that was developed by Elan and I believe that they will go into some detail on the issues related to developing that formulation later.

There was improvement in quantitative measures in all the ten patients, who were studied in this and there were no serious adverse events. We enrolled 22 patients who participated in pharmacokinetic studies of the slow released formulation in an open label safety study. And the treatment exposure in those 22 patients ranged from 6 to 42 months. There were a total of 52 patient years of experience in this group. There was long term efficacy in 16 -- that is, greater than two years of efficacy in 16 of the patients.

There was one grand mal seizure, which occurred after the patient had been treated for 24 months. Now, it was mentioned before that the major side effect of 4-aminopyridine is seizures. There is in vitro evidence suggesting that aminopyridine treatment increases both inhibitory and excitatory transmitter release in hippocampal neurons and in other areas.

That is likely to be the underlying basis of epileptogenesis. Seizure induction is a dose-related effect in animals. The early experience with this was in an outbreak of botulism poisoning in Birmingham, England. 4-AP was given intravenously and two patients in that group had seizures and drug levels at the time were estimated in the range of 35 to 90 nanograms per ml in one patient or 140 to 475 in the other.

There have also been cases reported by poison control in New York. A couple of these were reported in the literature and in one a drug level was available and it was 136 nanograms per ml.

In the concentration controlled trial that I already mentioned, the level in the patient, who had a seizure was 104 nanograms per ml. In the Dutch open labeled study, which I mentioned before, there were two seizures, but serum levels were not available in those patients. It has already been mentioned that there was a U.S. multi-center trial, which has not been fully reported. Three patients in that study had seizures.

The drug levels coincident with those seizures were 47, 7 and 140 nanograms per ml with the 140 nanograms per ml apparently related to an accidental overdose. There are also many anecdotal reports of seizures in patients taking various forms of 4-aminopyridine and I guess to clarify from

the compounding pharmacies, you can get either an immediate release formulation or you can get what is called the slow release formulation, which is basically 4-AP, mixed with carboxymethyl cellulose.

I guess I could add at this point as an anecdote that in our open label safety study, we had to terminate treatment last summer and 11 of those patients continued or were switched over to compounded slow release 4-aminopyridine and one of those patients had a seizure last fall after about three months on treatment. This is somebody who had not had a seizure in over three years of treatment with the other slow release formulation and then was rechallenged and had another seizure after several weeks on treatment and that patient has now been stopped.

Another patient, who I think Ron Cohen will mention, is currently in the hospital in Frederick, after presenting in status epilepticus. So, we had a rather disappointing experience in our patient group switching them over to the compounded drug.

In conclusion, epipletogenesis, I think, is the most serious toxicity that has been demonstrated. Seizures appear to be serum concentration related, but it is important to realize that the seizure threshold appears to vary quite widely from individual to individual. The toxic, the therapeutic margin, may be very narrow in some individuals.

The overall risk of seizures in MS patients, who are appropriately dosed and carefully monitored, is probably under 5 percent, which is comparable to the risk that was found with beta seron(?) treatment, which is a currently approved treatment for MS.

Then the last transparency, 4-AP may produce a modest improvement in some symptoms in some MS patients. For patients with no alternative treatments, these improvements may be highly valued. The efficacy of 4-AP in MS has not been proven in a large, well-designed trial.

I would be happy to take questions.

DR. JUHL: Questions of clarification?

Dr. Gilman, Dr. Katz.

DR. GILMAN: Chris, can you give us some anecdotal idea of what these patients were like on drug? They improved on the functional scales, but what does this really mean translated to the individual patient? Was the patient able to walk on drug and not previously able to walk? Or was walking greatly improved so the quality of life was improved? What did it do?

DR. BEVER: Okay. I used the term "modest" in the slide because we are not seeing the Lazarus effect, where a patient is non-ambulatory and you give them this drug and they are walking. We have had one patient like that and Andrew Goodman has had one patient like that. But those are patients,

who were sort of poised on the brink of just having lost a function and if you gave them back 10 percent, they would be able to do much more.

Typical would be improvement in strength and improvement in fatiguability and endurance. For those of you who don't deal with MS patients a lot, although we speak of this as a disease, a neurologic disease, one of the most disabling symptoms is the fatigue that goes along with the neurologic impairment that patients have. I think if you talk to a broad range of patients, who have been on this drug, that would be the main thing that people would report to you; that is, the woman who is at home is able to do more housework, is able to get up the steps.

We have an example of a patient here, who could walk with assistance around the house and on 4-AP was able to walk in the neighborhood and get out and just in many cases be able to do a full day's worth of activity; whereas, they couldn't without this drug.

DR. LIEBMAN: For your patients who needed a compounded medication, who compounded it? Do you know?

DR. BEVER: I do not direct patients to a particular compounding pharmacist and I can't tell you which pharmacist provided this drug. I have a list of about a dozen pharmacies and I tell patients to call them and find out what their prices are for what they need and go where the price is best. But

maybe that is bad advice in retrospect.

DR. JUHL: Dr. Katz was next and then Dr. Sellers.

DR. KATZ: I am interested in your conclusion that the seizures are concentration related. I am just not clear on what you mean. Apparently, seizures occurred at the concentrations from 30 to 140 or thereabouts. I am just wondering how you come to that conclusion or what you mean by it in some sense.

DR. BEVER: Okay. My thinking is that a given patient has a threshold level above which they will have a seizure and that if your drug level is below that, they will not, but that the level at which you can induce a seizure varies from patient to patient and the reason -- I mean, this makes sense to me in terms of MS because we have a disease, which is randomly causing inflammatory lesions in the brain. Some of those lesions are going to be closer to cortex in some patients than lesions are in others.

There are actually a couple of anecdotal cases of people, who had been doing well on 4-aminopyridine, who had seizures and we did on one of our patients and another patient that I am aware of had MRI scans, which showed that they had cortical lesions at the time of the -- that were new, basically, found after the seizure occurred and were not present on earlier MRI scans, although we don't know exactly --

DR. KATZ: So, you think there is an interaction

between disease location and propensity to have a seizure with treatment? In other words, you have to have a near cortical lesion to have a seizure with this?

DR. BEVER: Well, no. We can make a seizure in a normal person. So, it can't be just that simple. But I think that if somebody has cortical lesions, that probably increases the likelihood of their having seizures.

But I think -- I mean, really what you want is good, titrating up people to when they have a seizure so that I could say the threshold in you was this level and in me was some other level, we don't have data like that.

DR. SELLERS: You are touching on my question there.

Monitoring of the drug level, how routine is that and what is the availability of having levels done at a lab across the country? I mean, is it something that you have set up in your practice or --

DR. BEVER: Okay. The levels that were done in some of our studies were carried out in the School of Pharmacy at the University of Maryland. Jim Leslie set up an assay. That was done during the period of the concentration control trial and for some time after that. As far as I know right now, the only levels are from Elan and I am not sure of that. There may be another source for them. They can be done, but usually the turnaround time is in a matter of days. It

took a lot of logistical support in order to get levels back in three hours, which is what we required for the concentration control trial.

DR. SELLERS: It appears that we are looking at a drug that may have a narrow therapeutic index and in that case, it would most likely require routine monitoring of levels.

DR. BEVER: Well, we have thought about that. The problem is that you have some people who had a seizure at 104 nanograms per ml and somebody who also had a seizure at 44 nanograms per ml. So, I am not sure that therapeutic --

DR. SELLERS: Well, you were mentioning titrating the dose based on levels or based on therapeutic response to the drug?

DR. BEVER: Yes. Practically speaking, we would look at therapeutic response in patients and that is how we titrate it.

MR. TRISSEL: I believe you mentioned that you had several patients in your study who dropped out for some reason that was unspecified and you referred them to a compounding pharmacy. Was there no effort to get the Elan product donated for off-study use for these patients to continue them on?

DR. BEVER: WE went through a rather long and protected negotiation, which ended up in my getting an IND number so that we can do that, but it never occurred. We never got drug.

DR. RODRIGUEZ: How useful it was in cases where a patient had seizure, let's say, to try to prevent the seizure? I am talking about other -- in other words, epileptogenic control. Did you try that in some of the patients that you tried to titrate?

DR. BEVER: Okay. I guess the question is if a patient had seizure on 4-AP, would it be useful to put them on an anti-epileptic drug and then put them back on 4-AP. I guess there are two different aspects to that question. The first aspect is it has been tried, not by us. There is a practitioner in New York City, who has prescribed 4-aminopyridine quite widely and he had enough seizures so that he started putting people on concomitant treatment with anticonvulsants, but from anecdotal reports that I have obtained, he still had patients having seizures, even though they were on anticonvulsants at the same time.

The second issue is that we have actually reported a couple of cases where patients were given carbomazopine for trigeminal neuralgia while they were getting 4-aminopyridine and the patients reported to us without us prompting them at all, I promise, that they saw a decrease in efficacy. Theoretically, if you give a sodium channel blocker, that can undo some of the beneficial effects of the potassium channel blocker.

So, we may be somewhat limited in the drugs that

can be used along 4-AP to try to do this. Depacote, valproic acid would be one that has been suggested. That is the situation with the use of anticonvulsants right now.

DR. GILMAN: I would like to follow-up on Dr. Katz's question. I think the advent of seizures in any particular patient is the major concern here with respect to safety. So, the question is, first, do you know whether there is a higher frequency of seizures in MS patients compared to any other group that has tried all this medication?

DR. BEVER: Again, I can't speak in detail about the spinal cord injury studies, which I only know sort of superficially, but my understanding is that they have not had seizures in the spinal cord injury group --

DR. GILMAN: In Lambert-Eaton.

DR. BEVER: In Lambert-Eaton, I am less sure about. Dr. Sanders is here. He can --

DR. GILMAN: I have a communication that I will tell you about in detail later from one of the people at the Mayo Clinic, who did the -- who reported on the 1989 study in Lambert-Eaton Syndrome. They believed that seizures were very rare, as long as you keep the dose under 25 milligrams per day -- sorry -- four times a day. They believe that the blood level, in fact, is key. The question is whether there is a bigger variation in MS patients than in Lambert-Eaton.

DR. BEVER: Okay. Now, they are working with

3,4-diaminopyridine.

DR. KATZ: Yes, I know, and it is slightly different.

DR. BEVER: Our study was mentioned. We had one seizure out of 36 patients, who were each exposed for a month.

So, anyway, to get back to your question, I think that there probably is some difference in the frequency of seizures in different patient populations and I think, again, we are reviewing the evidence in MS. We came up with a number, something under 5 percent, 3 to 5 percent, something in that range. I think that is higher than has been reported in spinal cord injury.

DR. JUHL: Dr. Katz.

DR. KATZ: Yes. I just wanted to make a comment about whether or not an event is rare, as you suggest it might be with 3,4-diaminopyridine in the Lambert-Eaton patient. "Rare," I guess, is in the mind of the beholder. I don't know what the size of the cohort is that -- even though you showed me that -- what the size of the cohort is, but if you have 50 patients, let's say, even if they have that many, and you don't see a seizure, it could still be fairly common and it might have been missed.

So, I just -- sort of as a word to the wise. I guess we will hear about that.

DR. MC BURNEY: Dr. Bever, the patients now that

are on the medication, they are receiving it through an IND from a drug company?

DR. BEVER: No. The patients -- I had a group of patients who were in an open label safety study. The open label safety study was terminated by the sponsor. I applied for an IND in order to try to continue to be able to provide the drug to them outside that safety study. We were never successful and I got the IND, but I never actually got the drug.

So, those patients were given the option of going on the compounded drug and that group of 11 patients is the one that I mentioned, where we have had a couple of seizures.

DR. JUHL: When you say you couldn't get the drug, you know, the drug product from the sponsor, the same product?

DR. BEVER: Right. We needed to get the drug from Elan. That is what we were trying --

DR. JUHL: The drug product, the final formulation.

DR. BEVER: Right. And we were never able to get that.

DR. MC BURNEY: And that company is no longer carrying out the studies?

DR. BEVER: No. Elan is still the manufacturer of the study. They licensed the drug to Acorda and Ron Cohen will be talking to you later as a representative of that company.

DR. MC BURNEY: Thank you.

DR. JUHL: Other questions of clarification?

[There was no response.]

Thank you very much.

We will now move to Multiple sclerosis. Sharon Hamm, who is a senior vice president, Research and Development Technical Operations for Elan, to talk about formulation issues related to 4-aminopyridine.

Again, that handout was given to you during lunch, I believe.

MS. HAMM: Good afternoon.

I am Sharon Hamm of Elan Corporation. Elan is a leading provider of drug delivery technology. As a pharmacist, I understand both the art and the interest in compounding prescriptions.

My focus for today's meeting, however, is to help you understand why fampridine, which is also known as 4-aminopyridine or 4-AP, should not be considered for routine pharmacy compounding. I would like to provide you with some background understanding of fampridine and the particular difficulties associated with its compounding that could affect its safety and effectiveness in its performance, particularly in patients who are often quite ill and frequently on multiple pharmacologic regimens.

Fampridine, as you have heard, is a potassium channel blocking agent, which is currently in clinical development

for symptomatic treatment in multiple sclerosis and spinal cord injuries. The clinical development is conducted under an IND, sponsored by Acorda Therapeutics.

Dr. Ron Cohen of Acorda will address you as well following my remarks.

Although Acorda is responsible for the clinical development programs for fampridine, Elan has been involved in the dosage form development aspects of fampridine and we supply the clinical trial materials. We believe our experience in the development of the fampridine dosage forms is important to your understanding regarding its suitability for routine pharmacy compounding.

Over the last six years, we have conducted a range of formulation development activities with fampridine covering immediate release, IR, and modified release, MR, dosage forms in both capsule and tablet presentations while the preclinical and clinical development activities for fampridine were progressing.

From our immediate release development experience, we demonstrated product performance, which indicated linearity across a dosage range of 10 to 25 milligrams, a half life of approximately 3 1/2 hours, a considerable food effect with a maximum concentration that was lowered by 50 percent and an AUC that was lowered by 15 percent, a narrow therapeutic index, particularly evident with significant CNS side effects,

which appear dose related in MS patients.

Therapeutic levels, as you have heard, were on the average range, 20 to 70 nanograms per ml, with serious side effects often observed in excess of a hundred nanograms per ml. As Dr. Bever mentioned, this could vary. We experienced numerous formulation challenges in developing either the tablet or capsule dosage forms of fampridine.

For the tablet formulation, there were significant interactions with diluent, loss of potency on stability, which was directly related to temperature, humidity and container. For the capsule formulation, we saw significant excipient interactions as well, stability problems, which included loss of potency and unpredictable product release, along with drug migration into capsule shells.

This experience background led us to develop a specific modified release or you have heard sustained release formulation, which was designed to address some of these features, specifically the modified or sustained release product, provided the same extent of availability as with an IR formulation, although reduced the C-Max, thereby reducing peak-related side effects, providing minimum peak to trough(?) variability, if you would, smoothing out the curve, a lack of food effect, improved GI tolerability, twice daily dosing and a more stable formulation.

Even during this modified release development, we

continued to experience formulation difficulties, which was consistent with our IR experience. This included, again, polymer interactions, excipient interactions, container material interactions and degradation products.

We are aware of the availability of pharmacy compounded formulations of fampridine, both foreign and domestic. We required a random sample of fampridine from two different compounding pharmacies for analysis. We recognized that as these were randomly selected samples, they may not adequately represent the findings of a broader sample. However, we thought the findings would be of interest to this committee.

In the first sample you see here, identified as Colorado, we conducted content uniformity assessments of nine different capsule specimens. Although the target content here was 10 milligrams, actual content ranged from 8.8 to 15.6 milligram per capsule and would have failed USP content uniformity testing criteria.

Upon assay, four unknown impurities were identified on chromatograms, none of which interfered with the main fampridine peak, which was similar to a known standard of fampridine.

The second sample we obtained, identified as Maryland, again, provides a range of variability on content uniformity testing, which would fail standard USP criteria.

Although capsules were labeled as 8 milligrams, they contained a range of fampridine from 3.3 to 9.2 milligram, with a significant variability.

The HPLC analysis of this sample did not indicate any presence of impurities, unlike the prior ones. Both the Colorado and Maryland samples were selected at random and the age of these capsules relative to their date of compounding would not be known.

Although these represent a limited sample, the products demonstrated a failure of the compounded products to meet USP content uniformity requirements, showing significant inter and intra sample variability, both of which could possibly be due to poor homogeneity of the actives in the sample. Unknown impurities were also identified in one of the two samples.

These results are not surprising, given our own experience in formulation difficulties and development with fampridine. We would expect that these results would only worsen if assessed as part of a formal stability program.

To summarize, our experience has demonstrated significant difficulties in compounding fampridine due to excipient interactions, polymer interactions, drug migration into the capsule shell. In addition, we observed product instability with respect to temperature, humidity and container compatibility.

Recalling that fampridine's pharmacologic, pharmacokinetic attributes include a low dose, high potency, narrow therapeutic index, with side effects related to peak plasma levels, which include serious CNS effects, as you have heard, when combining the formulation difficulties of fampridine with its pharmacologic attributes and the intended patient population for its use, there are significant risks for adverse effects.

We hope that you will seriously consider this background as you deliberate the suitability of fampridine for pharmacy compounding.

Thank you.

DR. JUHL: Well, let me ask the question that is on everybody's mind. Compounded products have significant risk for adverse effects, but, yet, your company took a group of patients who was on your product and hung them out to dry. Why did that happen?

MS. HAMM: I would admit that this is something that I am going to let Dr. Cohen address in more detail as he comes to the podium. It is really not quite as simple as it sounds and it just so happened that we were in a state of transition at the end of Chris's trial, both in terms of some formulation activities, as well as transferring of the ongoing clinical research activity to Acorda. It really was a timing unfortunate circumstance in that particular situation,

but I am sure Dr. Cohen can address that as well.

DR. JUHL: Okay.

You understand one of the things we are looking for is the -- for you to inspire us with confidence and that doesn't go in the right direction for us.

Other questions of clarification?

MR. CATIZONE: Mr. Chair, while awaiting the specifics from our next presenter, let me ask the question what course of therapy is left or what alternate is left to patients if the medication is not produced by Elan or not made available? Are there any alternative therapies except for the product to be compounded by a pharmacist?

MS. HAMM: You are asking if I would know if there are alternative forms available? I mean, in a domestic sense, I am unaware of any other source.

DR. JUHL: The information that you provided us is not quantitative in terms of impurities, migration of the capsule, those kinds of things, nor have we seen serum concentration versus time to see the effect of your formulation. I presume that some of that is proprietary? Is that information -- has it or will it or is it being submitted to the Agency so that can be scrutinized?

MS. HAMM: Information with respect to the trials and data that would have been obtained from them would be under the IND. Additional information in terms of the testing

outcomes on the compounded samples and any of those details, we would be glad to provide in a confidential manner.

DR. JUHL: I was more interested in your product because there wasn't any information about that. We have more information on the compounded product than we have on yours.

MS. HAMM: Sure. It is in the IND and it was because of the proprietary nature we chose not to disclose more detail today.

DR. JUHL: Okay. I guess we would have to look for the Agency not for disclosure of the information but for scrutiny of the information to be sure that it corresponds with the sense of the qualitative information we have received.

MS. HAMM: Thank yo.

DR. JUHL: Any other questions?

[There was no response.]

Thank you.

Our next presenter is Dr. Ron Cohen, who is president and CEO of Acorda and I guess Andrew Blight is presenting with you as well?

DR. COHEN: Actually, Dr. Andrew Blight is here and can answer questions, but I will be presenting.

DR. JUHL: Okay. Great.

DR. COHEN: Thanks.

I am going to depart from my prepared text for just

a moment to say that since this issue has come up, I will address in the course of my remarks this issue about the compounded formulation, switching over from that long term study of Dr. Bever.

Thank you and good afternoon, everyone. My name is Ron Cohen and I am a physician and the president and CEO of Acorda Therapeutics. Acorda is a biotechnology company, which is focused on developing therapies for spinal cord injury, multiple sclerosis and other disabilities of the nervous system. Acorda is sponsoring, as you have heard, clinical development of an oral tablet form of fampridine for both chronic spinal cord injury and MS under INDs in compliance with FDA regulations.

As you have heard from Dr. Hamm, the formulation of fampridine that is used by Acorda was developed and is being manufactured and supplied by Elan Corporation. Acorda began its clinical development of fampridine in 1996. Initially, we used an immediate release capsule formulation, which was formulated for us under good manufacturing practices by an experienced pharmaceutical subcontractor.

In the course of this program, we were made aware by our subcontractor that fampridine is an unusually reactive compound and that this reactivity poses significant difficulties for manufacture of the stable formulation, using conventional approaches. Our initial formulation effort, therefore, took several months longer than we originally

anticipated. In addition, we were concerned by numerous reports from patients, clinicians and the scientific literature that immediate release formulations gave significant variations in plasma levels and that these variable plasma levels led to unpredictability of both therapeutic effects and adverse effects.

We subsequently investigated Elan's sustained release formulation. We concluded, based on Elan's chemistry, manufacturing and pharmacokinetic data, that Elan had successfully translated fampridine from a compound with significant problems of dosing and side effects to a potentially acceptable therapeutic agent.

We, therefore, entered into a collaboration with Elan, which permitted Acorda to deduct clinical development of this formulation for both chronic spinal cord injury and multiple sclerosis. We also obtained orphan drug designations for both indications to help make it economically feasible for us to develop the compound.

To date, we have completed three clinical trials of fampridine and spinal cord injury and we are sponsoring this year further trials in both spinal cord injury and in multiple sclerosis. We have not yet published these data, but they are in the process of being submitted to the Agency under our INDs.

Based on our own experience and on extensive

discussions with clinicians and patients, we believe that the Elan formulation is clinically useful. For example, in a Phase 2 double blind placebo controlled clinical trial that we sponsored, involving 60 subjects with chronic spinal cord injury, we were encouraged to see apparent improvements in outcome measures, including spasticity, clinicians' global impression and control of bladder, bowel and sexual function.

In addition, we interviewed 12 patients, who had experience of both Elan's formulation and the compounded formulations of fampridine. Without exception, these patients said that they tolerated the Elan formulation better and experienced fewer side effects.

However, there do remain issues concerning establishment of both safety and efficacy of fampridine that must be resolved in additional properly controlled and documented clinical trials. We have become aware that increasing numbers of people with multiple sclerosis and spinal cord injury are experimenting with pharmacy compounded formulations of fampridine. We understand that many of these people believe that they receive benefits therapeutically, but we are also aware that there are numerous reports of side effects and significant adverse events, including grand mal seizures and even status epilepticus.

In addition, both physicians and patients have expressed concerns to us regarding what they perceive to be

inconsistency and unpredictability of the effects of pharmacy compounded formulations. For example, I received an urgent call from a hospital pharmacist and physician last month, regarding a patient with multiple sclerosis, who had been admitted two days earlier in status epilepticus.

You heard earlier -- this patient was alluded to by Dr. Bever. This was a patient who had been in the long term study sponsored by Elan with Dr. Bever. I think he had been on the compound for about three years. The Elan formulation, without incident, was then switched over when that study was terminated and within approximately six months had this experience of status epilepticus.

At the time I discussed this his physician, this was two days after admission and the patient was still incoherent and unresponsive, although he has since come out of the hospital.

This patient had experienced tremendous rigidity of his legs, which made it impossible for him even to sit in a wheelchair. He had tried every available anti-spasticity therapy without effect and got relief of his symptoms only from fampridine.

To respond now in more detail to the question that has been raised, the issues surrounding the supply of the Elan formulation here were, in fact, a matter more of timing and circumstance than anything. At the time that the study was terminated, Elan was in the process of transferring its

entire dossier, the INDs, all of the documentation, to Acorda.

This is a process that actually took the better part of a year for us to get all the information in house and then assimilated in a way where we felt we had a grasp of it. In addition, this is a drug that is in development. So, we continue to need to have Elan formulate the drug to order so that when a given supply has been -- we run out of a given supply, we then have to place another order for the additional studies. In the process of all that and assimilating it, we felt that we really didn't have the wherewithal to jump in and continue the study.

We needed time really to get up to speed ourselves and then to work with Elan to supply. So, in the process, we did wind up supplying at least one patient with drug because we had enough drug in house for one patient. That patient actually is here with us today and would be available for comment. But, unfortunately, we were not able to get up to speed in time to supply this patient or others.

I will continue my remarks and inform this panel of what our intention is regarding future studies of this kind.

To continue with my prepared remarks in this regard, several leading neurologists, in addition, have told me directly that they have patients who have experienced seizures

and as this panel has heard, on pharmacy compounded fampridine, three of these physicians independently have told me that they most often see problems when patients perceive that they are experiencing a waning of therapeutic effects within a given prescription. Then they self-medicate, doubling or sometimes even tripling their dose on a given day, at which time they sometimes run into problems with adverse events and even seizures. This is the impression that these physicians have given me and these reports are consistent with the data that you have heard earlier from Dr. Hamm, showing marked intra and inter sample variability, as well as the presence of impurities and loss of potency over time of pharmacy compounded formulations.

The key directive of the Hippocratic oath is first do no harm and I believe that all of us as health care providers are concerned that any potential pharmaceutical agent for serious or life-threatening conditions in particular be developed as rapidly as possible, but at the same time maintaining accountability and responsibility and a concern for patient welfare.

It is difficult to credit adequate accountability and responsibility to the current situation in which thousands of patients receive variable and undefined doses of fampridine without documentation or adequate assurance of safety and efficacy.

We recognize the desire of patients with seriously disabling conditions to have access to an agent that they believe offers some improvement of their condition and we recognize that Acorda finds itself in a position to offer a responsible alternative to the current situation.

With this in mind, Acorda has informed CDER that if fampridine is not placed on the list of allowable substances for compounding, Acorda would be willing to sponsor a long-term expanded access clinical study of our formulation of fampridine within the appropriate regulatory framework.

In such a study, which may require cost recovery, Acorda would provide its formulation of fampridine in an open label fashion to patients who would be deprived of pharmacy compounded fampridine. we would collect data related to safety of long-term administration and we would continue to sponsor this study while Acorda conducts additional Phase 2 and 3 studies in preparation for filing a new drug application or NDA.

If, however, the compounding of fampridine is allowed, we will be unable to offer such a program. Acorda and Elan already have invested several years and many millions of dollars in research and development efforts to develop a safe, reliable form of fampridine in compliance with recognized drug development procedures.

If pharmacy compounded fampridine continues to be

made available, we would not be able to justify the significant additional investment of time and resources that an expanded access study would require. Moreover, we would have to seriously review whether it would be economically feasible for us to continue clinical development of this compound. We believe that such an outcome would poorly serve the long-term interests of the patients and their health care providers, who deserve to have a therapy that can be prescribed with assurance of reliable dosing, appropriate indications for use and overall safety and efficacy.

Such assurance can only be obtained for this drug if it is developed under INDs and approved by FDA under an NDA.

Thank you. And I would be pleased to answer any questions you may have.

MR. CATIZONE: Dr. Cohen, if we can, can we return back to the Hippocratic Oath, in which you quoted your remarks and let me ask the question. Doesn't it seem logical that the patient that you talk about in the study that is currently hospitalized, that the hospitalization was caused in some part to being stopped from the medication they were stabilized with and that the compounding pharmacist supplied a medication that was unavailable to that patient?

DR. COHEN: I am not sure I understand your question.

MR. CATIZONE: Any patient that is stabilized,

particularly a patient with a severe illness, on a medication, and whose therapy is stopped immediately with no recourse of that patient to access that medication is going to have complications with their disease state. I can't believe that by the pharmacist compounding that medication alone, that was the sole reason for the hospitalization and the epileptic seizures.

DR. COHEN: There is no way in fact to demonstrate on an anecdotal basis that a given event is due to a drug or is not due to a drug. Obviously, we look at the population. We look at the trends and the patterns. My concern is an overall concern, not specifically keying off this patient, but rather on the overall experience in the data you have seen today, which demonstrates that the pharmacy compounded formulations of this drug are widely variable and if we put those in the hands of physicians to try to dose their patients appropriately, we really have not given them any compass whatsoever with which to work with a compound that is known to have the potential for these sorts of effects.

So, whether or not in this particular case, the patient's status epilepticus was directly related to having been on the compounded drug for six months, my concern is a larger concern and that is that you have an absolutely uncontrolled situation out there, an undocumented situation where thousands of people have access to very variable and

undocumented, non-GMP formulations of this drug. And this is a drug that needs to have as much information as we can put into the hands of physicians and the patients in order to make it a reasonable therapy and to mitigate the known risks.

MR. CATIZONE: So, I have an understanding of your closing comments then, is Acorda and Elan saying that unless there are economic incentives provided to the company to make this economically feasible for your two companies, you will not conduct extensive clinical trials to prove this medication is worthwhile and useful, but in a small clinical trial in which a limited number of patients were participating, that guarantee to provide the medication was not carried through or honored and at least the few patients were forced to use this inferior product because your company said they couldn't produce it because of some sort of snafu in the transition.

DR. COHEN: I think that is an interesting interpretation of the events, but it does not accurately reflect what my statement was meant to convey. You know, we are talking about a drug for which there are intonations of efficacy. As Dr. Bever told you and as you have seen elsewhere, there is still to date not a single large, well-controlled study that gives conclusive evidence of efficacy. So, to begin with, although personally I do believe that the drug has efficacy and is a useful clinical compound, that still remains to be

proved, whether I believe it or not, whether you believe it or not.

Secondly, it is a compound with demonstrable potential for serious toxicity and putting those two elements together tells me that if we are going to do this responsibly, we need to go through the process of controlled clinical trials, dosing studies, so that we know what we are doing and with a formulation that is a controllable formulation, that gives reliable plasma levels. To me, that boils down very simply. In terms of the intonation that we left patients high and dry, I reject that information.

You know, we are a small company and we are doing our very best to do a good job of bringing this compound to the clinic for our patient populations. At the end of the day, that is why we are here. In terms of economic feasibility, we live in a world of real economic constraints. I don't think I have to tell anyone here what it costs to develop a drug in an appropriate fashion. What I am saying is that if compounded 4-AP is out there on a widespread basis, where we have basically uncontrolled formulation and wide access to it, it will make i t much more difficult for us to convince our investors that they ought to invest in us to carry out this program because I answer questions from them everyday about why are you developing this drug in the right way when you have got all this stuff out there that people can just

get and no one is investing in clinical trials out there.

DR. JUHL: There are a number of fallacies in what you are going through here and I want to pick them one at a time.

Are you saying to us that you are unable to mount an economic effort to conduct the trials without the revenue stream that you would have from an expanded access program?

DR. COHEN: No. What I am saying is that we are proposing to make an expanded access program available and --

DR. JUHL: I understand that and I appreciate that. I really do --

DR. COHEN: And within that expanded access program, we certainly aren't going to make any money off that. In fact, we have concluded that even with cost recovery, we are going to have to invest significantly additionally to carry out that program. So, that is an issue of actually doing a study that we otherwise would not be required to do and would not choose to do. We would do it because we recognize that the patients out there do need an alternative and they do need a drug that is better controlled and better defined.

So, we are willing to do that. We are not going to make a dime off that nor can we, frankly, under the regulations. We are going to invest additionally to do that study.

DR. JUHL: Here is the part that I don't understand.

If you do the study and get the drug approved, then that is an NDA'd product for which pharmacy compounding would not be allowed. So, how does that adversely effect your economics when you get into the market?

DR. COHEN: I have to say that I am not aware of -- if we get an approval, I am not aware that the pharmacy compounded would be -- compounding would be disallowed at that point under the current regulations.

DR. JUHL: Under Section 127, the pharmacist cannot make copies of a commercially available product.

MS. AXELRAD: Excuse me. That is not strictly speaking correct. They cannot compound regularly or an inordinate amount --

DR. JUHL: Unless there is a significant medical need.

MS. AXELRAD: -- copies of a commercially available product and we have yet to define what it means to be regularly or an inordinate amount. Certainly, some compounding of commercially available products would be allowed under our regulations. In fact, don't forget that one of the criteria for the bulk drug substance that you can use in pharmacy compounding is that if it is the subject of an FDA approved application, then you can use it to compound.

DR. JUHL: There has to be a valid medical need above and beyond just changing a milligram or two. I mean,

the discussion in Congress I thought was rather clear to prevent that.

MS. AXELRAD: They don't specifically use the words "medical need." There are issues associated with what level of need there is that we will be addressing in the general regulations.

DR. COHEN: So, what I understand about the situation is that it is not cut and dried. There is uncertainty. There is nothing in my experience that scares away investors faster than uncertainty. We rely on investors to allow us to continue our programs. We are not a revenue generating company as yet. We are an R&D company, research and development. So, all the R&D that we do is funded by the good will of the investors, who believe that we are developing important products that ultimately will make it to market.

That introduces more difficulty for us to the extent that there is more uncertainty. However, let me say that that is still not my chief concern. I mention it because it is a real concern and we will have to seriously review what -- how to move forward, where we choose to put our investment dollars if that uncertainty continues to exist. But that is not my chief concern. My chief concern is that we truly have a situation with a compound that in my view and our view ought not to be compounded because what we have seen is that these compounded formulations are nowhere near as reliable

as they need to be to ensure a standard of safety, a reasonable standard of safety for our patients and dosing.

We have a formulation that we believe is much superior in those regards and we are willing to make it available and, in fact, we are willing to invest additionally of our time and resources to make it available in the case where there were no compounding of 4-AP.

DR. JUHL: I appreciate the GMP produced drug is going to be better than a compounded drug. The question is is a compounded drug better than no drug at all?

DR. BEHRMAN: Dr. Juhl, could I make a comment because some of what we are debating right now is very common to life-threatening diseases, where there aren't good therapies and there are new therapies coming along and maybe people have access and maybe people don't. It is something the Agency struggles with a lot. Unfortunately, it is not uncommon to see circumstances where people are left without supplies and that is something that the Agency is becoming better at trying to prevent. But, obviously, it doesn't always work.

But the issue before us that concerns the Agency is not what is economically feasible for a particular company or -- well, in particular, that, but rather is something that may or may not be provided to the public safe. In other words, as Dr. Woodcock discussed yesterday, when we think about access,

any kind of access, one of the first concerns we have is that the safety of the patients is being protected.

So, for us, it is a question of should this substance be on the compounding list or not. That has to be answered before we can then turn to how to develop it safely and by whom and also ensure that during that process, there is access for those who need it. But they are really two separate questions and the ability to -- or at least it doesn't so much influence our decision about whether to make it available, that other mechanisms aren't available if we believe it is not safe.

So, for us, the real issue, is it safe, can it go on a compounding list or not. If we answer the question that, no, it can't be compounded, then we have to tackle the question of how can we get it developed and how can we make sure that there is appropriate access.

DR. JUHL: The different quirk here is that unlike other compounds that are being developed and are new, you don't have a few thousand patients that are already on it. This is the issue here. We have patients who are already on it, who we have to be concerned about.

Unfortunately, I mean, I understand the Agency doesn't deal with economics, but in order to mount the effort that would be required to provide the entire country with this drug, there has to be some confidence in -- at least

from my perspective -- in the company to be able to do that. The only example of performance we have here is was unable to get drug for 23, 29 patients, one of whom ended up in status in the hospital.

So, I want to be sure that --

DR. COHEN: If I could comment on that?

DR. JUHL: Let me finish, please.

I want to be sure that if this committee recommends that they ought not be put there, just as our discussions this morning, that there is a place for patients to turn and they won't get caught up in what you described as a year's worth of bureaucracy to transfer papers and the patients didn't come first in that situation.

DR. BEHRMAN: Well, I think to a certain extent then it is our responsibility to assure you that -- and this is something we are very familiar with and good at -- that we will represent you in those negotiations with the company and satisfy ourselves that the distribution program, to the best of our ability, obviously, because as Dr. Woodcock mentioned, we can't force any company, but we are fortunate that we hear an assurance that, in fact, such a program would be developed, but that you trust us because we are committed to doing that, to making sure that entry criteria, inclusive criteria, are reasonable and that the people who need the access are the ones that get the access and get it in the

safe manner.

DR. SELLERS: I am trying to understand what you are describing, Dr. Juhl. If the company was no longer to obtain the drug that was being manufactured, wouldn't obtaining it from a compounding pharmacy be a better choice than cutting off the drugs altogether?

DR. JUHL: Well, I think that is one of the questions.

DR. SELLERS: Right. And I feel like we are implying that they did the wrong thing by providing a compounded product, but they didn't necessarily know at the time that they were providing a product that wasn't of the same standard as what the patients were getting.

DR. JUHL: Yes. There was no alternative at that point.

DR. COHEN: Actually, if I could add to that because that really was along the lines of what I wanted to say. You know, we are all learning as we go along. It is a development program. So, we continue to learn. At the time -- I am sensitive to your concern and certainly retrospectively how one might interpret the fact that you have this group of patients, who were on drug and then the company cut them off and they went to compound and then we have these problems.

I think the reality is more subtle and more complicated than that in meaningful ways. If we had -- I think if we had had the understanding a year ago that we have

now, after having the benefit of studied the circumstance more, having become more aware of the compounding issues and looked into it in more detail, having taken the time to interview physicians in more detail and bringing ourselves down the learning curve, we might well have had a greater sense of urgency amid all of the priorities that one has in the company even as we were transferring this whole portfolio, which does take time.

I would also say that that was a one off event. We are talking about a business alliance, which occurred once in which Acorda entered into an alliance with Elan and consequently there had to be some time to transfer information and documentation. That is a one off. At present and for the foreseeable future, Acorda has the exclusive license to all of Elan's technology related to this drug and to -- and the exclusive license to develop it for multiple sclerosis and spinal cord injury.

So, we do not anticipate a repeat similar event in which there will be any lengthy interruption of the chain of command, as it were, or chain of activity. So, that is an issue that is behind us. I think moving forward what we are saying is we have spent a good deal of time over the last few months studying this, discussing it with Elan in great depth and concluding that we needed to offer to do a large expanded access study.

We are quite capable of doing that study and Elan is quite capable of supplying sufficient drug for that study. As with anything, it is a matter of timing, intent, planning and then execution. I think looking back over the last year is not going -- I would submit to you that that is not instructive for learning what we are capable and willing to do in the future because it really was a one off situation of transfer of responsibility for the project.

DR. BEVER: I apologize. I don't know whether you take comments from the audience.

DR. JUHL: We usually don't, but go ahead.

DR. BEVER: I just want to clarify that we are talking about a group of patients who were in a clinical trial. They were not in a compassionate use program or anything like that. There was never, as was intimated earlier, any promise to these patients that there would be ongoing availability of this drug. It always, with Elan and Athena and Acorda was sort of extending bits at a time. And as you know, the consent form that patients were signing basically says that this sponsor has the right to terminate the trial at any time for any reason and patients were told that.

I mean, I was concerned about that from the beginning and tried to make that clear to the patients that this was a research study and it could be terminated. I mean, that was something that we just dealt with. We tried to deal with

it as best as we could and looking back on it, it probably wasn't the best way of doing it, but we know more now.

DR. JUHL: Perhaps it is just one of my pet peeves, but having served on several IRBs, that is one of the things we always put in the consent form as to what happens when the study is done.

MS. LA FOLLETTE: I would just like to make a comment. If Acorda is successfully continuing with their IND studies and then successfully file an NDA -- at our training session yesterday, 90 percent of ADRs that are reported are from companies and that is a benefit if a product goes commercial, that you will actually have a history and you will have information, which we haven't been able to really nail down with pharmacy compounding, how adverse reactions are going to be reported or if they will.

MR. TRISSEL: What is the time span of your development plan now? How many years more in development do you anticipate? It sounds like you are pretty early on.

DR. COHEN: You know, I am quite hesitant to go on record predicting what the length of the development program will be. I think we all understand the vagaries of clinical development.

MR. TRISSEL: It is not a year.

DR. COHEN: Well, you know, it is not a year, but I don't think it is five years. I don't think it is ten years,

but, you know, at the end of the day, we don't know until we get into the clinic further. We have done a couple of Phase 2 studies. We are going to be doing more Phase 2 studies this year.

If those go well, then our plan is to get into pivotal studies next year. I say this emphasizing that this is our current plan and it will entirely depend on the actual results of the studies that we see, which is why we are doing the studies, of course, to begin with.

MR. TRISSEL: As it applies to the expanded access program that you are offering, apart from the patients that are going to be on your clinical trials, how many patients do you anticipate that you will have to supply with drug during this time frame from the next two to five years, two to ten years in terms of thousands? How many patients do you think you are really talking about?

DR. COHEN: Here, again, you know, I am reluctant to speculate on what we are talking about. I will tell you that we are capable and prepared to supply as many patients as we believe are out there. I will tell you that it would be many thousands, many thousands of patients, as far as we know, who are out there. We would be prepared to supply them, those who are taking compounded fampridine.

MR. TRISSEL: And you would be ready to start this in what length of time, do you think?

DR. COHEN: Well, again, I think -- as I indicated, we are going to look to see what the outcome is of this panel's deliberations, of the FDA's deliberations, because truly at the end of the day if the compounded drug is allowed to be -- or if the drug is allowed to continue to be compounded, we really will not be able to do the study. We just will not be able to muster up the investment in us that we need to do the study. It is just a fact.

MR. TRISSEL: But if we don't have a time frame for when you can begin delivering that, then we --

DR. COHEN: We could begin delivering it as soon as six months.

MR. TRISSEL: As soon as six months.

DR. COHEN: That is, you know, give or take, but that is a reasonable time frame. If you wanted to say by the end of this year, I don't think we would be far off.

DR. LIEBMAN: When the patients who were told to get their medicine compounded because the study could no longer supply it, were they instructed that this is a very sensitive kind of drug and you need to go to a pharmacy, who is skilled in doing that or was the issue of find the cheapest guy around, such that, you know, it doesn't matter. Price is the issue.

DR. COHEN: That is just an area that we have never been involved with. Maybe Dr. Bever might want to comment on that.

DR. LIEBMAN: Dr. Bever, I don't mean to beat on you. If you were referring a patient of yours to another physician, would you say here are a list of four physicians. Call and get the cheapest one or would you say these are people I know are qualitative and I would strongly recommend these people because they are good at what they do?

DR. COHEN: I should point out that the two samples that were analyzed by Elan that Dr. Hamm presented earlier, the two samples the pharmacy compounded, were obtained from two of the larger suppliers, as far as we know and two of the ones that we believe to be the most reputable, again, I don't know how you make those determinations, but these were not -- both of these places advertise on the Internet. Both of them, as far as we know, distribute a fairly large number of prescriptions annually of fampridine.

And those prescriptions were quite variable in their quality, as you saw.

DR. LIEBMAN: I don't mean to be argumentative. Just because they make a lot of them doesn't necessarily mean that they are skilled at what they do. It only means they make a lot of them.

DR. COHEN: No argument, but then I think one has to face the question of on what basis does the population at large and physicians at large make the determination of what is a high quality producer and what is not. I think,

in fact, what happens is people are all -- as long as compounding is allowed, people will obtain the drug from whoever is supplying it and I don't see a good way of regulating that without, in fact, regulating the development of the drug.

DR. BEVER: I will repeat my comment in the microphone that I gave before. And that is we did just give a list of pharmacies to patients and tell them to find out what the cost was. My problem is that a clinician is -- is that it is not easy to get data on compounding pharmacies that would allow me to distinguish a good one from a bad one. We had picked what we thought were fairly reasonable ones through patients to get drug that was analyzed by Elan and that didn't help us.

DR. PECK: You are going to have to be careful about listening to me because I may generate some thoughts by you that you will disagree with.

Data was prepared by your firm or Elan, which talked about the poor quality as was judged by weight variation and so forth from the two sources of this compounded product. These information were given to us and then there were some assay -- limited assay data presented.

You will probably say we don't have to do this, but you have not presented anything that would indicate the superiority of either the capsule or the tablet formulation showing that there is diluent interactions, migration into

the capsule shell, which is not uncommon. Many drugs do this. While you can say, however, that the Agency will be given this particular information, but we as a committee have to sit here without this information and make some decision, which is a little bit in favor of you in terms of no compounders can do their work.

I am not sure whether I am clear as to what you were saying out of your letter.

DR. COHEN: If you could clarify the question that you want me to answer in that?

DR. PECK: Do you have data that demonstrates that your products are superior?

DR. COHEN: I believe that Elan does, based on our investigation of Elan's portfolio and Elan's data.

DR. PECK: But that would be available probably only to the Agency?

DR. COHEN: Sharon? Yes.

DR. KATZ: Yes, I think one of the great advantages of requiring that studies be done under an IND is that there are strict standards, as you undoubtedly know, about the strength and the identity and the purity of products that are permitted to be given to people under the IND. Without speaking specifically about any product, I think in this context, one of the great advantages is just that, that we have seen that there is considerable variability in the compounded

products and we have standards that sponsors are always required to meet for the composition of products under INDs, just as a generic statement.

DR. JUHL: We have been told that the new product meets these standards and exceeds that of the compounded ones. But we are asked to trust that without data, I guess, is --

DR. KATZ: Well, as Dr. Behrman said, I mean, part of this -- to the extent that certain things are not -- are confidential under the IND and can't be discussed in public without the permission of the sponsor, that is a large part of what we do.

As she said, you will have to consider whether or not you trust us to do our job so that we would permit a product that meets our standards under the IND. Again, it is what we do. We do it everyday and we think we do it well and we have standards that are sort of public and folks have to meet them if they want to give a drug out under an IND.

DR. JUHL: Is that satisfactory, Garnet?

DR. PECK: Yes. I wanted a clarification of this particular situation and the judgment and the data that is available. The IND situation is very important to the development of new drug products and there are certain things that are in there that must be retained in confidentiality. But I don't like mixing economics with this confidentiality.

That part -- I am trying to separate that to evolve good products.

DR. BEHRMAN: We are really not -- we, FDA, are not thinking about the economics. We have one decision to make with your help, which is whether or not this product should be on the compounding list.

The second decision is the IND development and actually they are in a way unrelated. The Elan product doesn't have to be superior. As Dr. Katz said, it has to meet our standards. We wouldn't be particularly interested in the comparison, in fact. But we are not particularly worried about any company's economics right now. We are worried about the safety of the patients who will get these drugs.

MS. AXELRAD: I was just going to comment that people that are here from the Review Division weren't here this morning during the discussion, but it was sort of my understanding that we discussed the possibility of whether something should be put on the compounding list or not put on the compounding list, with the understanding that if it was going to be used, it would be done under an IND and we didn't have any information on any formulation of it at that time. We had some generalized safety information from the literature, but I think, certainly, the committee's vote with regard to DNCB was that it should not go on the list and that you would rely on the agency to make sure that if it was made available under an IND, that

it was -- that an appropriate quality product was made available and we sort of indicated that we would be carefully considering the chemistry, the impurities and other issues associated with that if we were to allow it under an IND.

So, I think the discussion that we had this morning sort of relates to what we are talking about now and if we are talking about the same situation and we would be looking at the product, the division would be looking at the product very closely under an IND and under any kind of an open label trial.

DR. JUHL: I think the one thing that is different, at least in my mind, I am greatly appreciative of the company's offer to have an expanded access program under an IND where we can collect more information. My concern is your ability to deliver and the past experience made me real nervous because we have patients out there that I think are doing better on the drug than they would do without the drug.

There is no question they would do better with the manufactured product than with the not manufactured product. I want to be confident in your ability to do that and you are essentially putting the gun at the head of the patients and saying either do this or we pull the trigger. I think the committee is reacting to that difficult decision. I am not arguing with you. I understand, but it is an uneasy one

for the committee --

DR. COHEN: Well, it is an uneasy one to hear fed back that way because it certainly -- we certainly don't intend it to come off that way nor do we feel about it that way. You know, it is not a -- it is really holding a gun to our own heads if you really want to put it that way.

DR. JUHL: I am reacting to your tone and your forcefulness on the do this or we are out of here kind of thing.

DR. COHEN: Then I willingly stand down from the tone and -- but still want to emphasize the point that it is not a question of us -- of do this or else by any means. We would not be so bold as to attempt to come before this panel and come off that way. It is simply a question of what we are trying to do in good faith, which is to assess what can we do and under what circumstances can we do it because we have our own constraints back home in terms of what we are able to do.

In analyzing that, our best judgment in good faith is that we are able to -- we would be able to supply the drug in a large expanded access study and we want to do so and we are willing to do so, that in the event that compounded drug continues to be unavailable, we will not be able to pull it off. And it is not a question of want to or not want to. We simply won't be able to pull it off.

If I didn't convey it that way, I apologize. That is what the reality is.

DR. JUHL: Yes. And I understand that and I appreciate you being forthcoming and not beating around the bush. Let me put it that way. But that is a decision we end up being -- you understand our --

DR. COHEN: I understand.

DR. RODRIGUEZ: I have concerns about some of the data that was presented and the concerns are not on the data per se, but on the implications of the data. When you have some things in which the actual sample is one-third of the dose and we have such a narrow type of safety, I just wonder what is going to happen in the meantime with this information because we are talking about safety and we are talking about there are a lot of people taking medication, who may cross the state line and go on some other compounding pharmacy and have been used to a 3.3 milligram and end up with the 9.2 milligrams for 8 milligram capsule.

Those things just worry the hell out of me as I sit over here thinking as a consumer to put it bluntly. So, I like the fact that you found that. We have lacked this information in many of the other products. We are trusting the fact through the Agency that this was conducted in an unbiased way and then the information is even if we go ahead and say there should be no compounding, for example, there

is going to be a lag in between. This information is, quote, unquote, your information and the question is what do you do with that information in the meantime because the people who use this medication are pretty much I would say involved in their destiny and if they were to find out that there were just differences in between the preparations, they will at least demand that that information be available to them.

Just a commentary.

DR. JUHL: Loyd, perhaps you could comment on the extrapability of those findings. I know there was one study that was published in your journal that showed maybe 10 percent, plus or minus, was about as good as you could expect under the best conditions for compounding. Here we have capsules with very small milligram amounts. What is reasonable to expect?

DR. ALLEN: There is no question those are outside. In fact, pharmacists that compound are required to meet the requirements of the USP for their products and clearly those are outside the limits. According to Phadema(?) 1997, the USP general chapter on compounding, which up until now has been an informational chapter, now moves down into the enforceable area and that process is ongoing right now.

Compounded pharmacists must meet the requirements for the preparation of a product. If there is a monograph in the USPNF, it has to meet that. If not, well then it goes

to the general guidelines of the general chapter. And we are looking at generally -- you know, most stability studies and things like that, plus or minus 10 percent of the target quantity of drugs. This would then -- if an individual pharmacist is not performing to that level of expertise, then that would fall into the enforcement agency, you know, the state boards, et cetera, in order to investigate that.

So, you know, clearly, that is outside the area of accepted practice, because plus or minus 10 percent is what is normally reasonable.

DR. JUHL: I wonder if I could ask Jane, does the MOU with the state boards include provisions that lead a board to investigate this kind of detail or maybe I could ask Carmen the same question.

Do you expect boards of pharmacy to go out and purchase samples, do the analysis and do a quality assurance in that fashion?

MS. AXELRAD: I would sort of have to defer to Carmen about whether they would actually go out and purchase samples, but I would say, certainly, at least, we don't have an MOU in place or anything right now. Certainly, the way we are dealing with enforcement issues is if we became aware of a situation through one way or another of something that was really out of compliance with the USP chapter on pharmacy compounding, we would probably want to consult with the state

in which the problem was identified and between us decide what kind of an appropriate enforcement action would be taken.

But I don't think we are doing a lot of inspecting right now of compounding pharmacies. Because of the uncertainty, we don't have any regulations in place and we are in the process of implementing it. But I don't think that we, ourselves, are doing a lot.

DR. JUHL: Would this information that has just been presented be fed back to the appropriate state board or to the pharmacy that produced these products in an effort to improve?

MS. AXELRAD: It could be if we had specifics on -- we would have to have specifics of what pharmacy -- specific information about it.

DR. SELLERS: Loyd, this is directed more towards you, but if compounding pharmacists are supposed to be meeting USP specs, how do they know if they are meeting those specs?

DR. ALLEN: Basically, there is no requirements that they have their products tested. What it is based on is whenever you get a certificate of analysis, where the product is 98, 99 percent pure as far as active is concerned, and then you have a formulation -- let's say you are preparing 100 capsules. Okay? 25 milligrams each. Well, then you would weigh out 2.5 grams plus your excipients, prepare the 100 capsules at one time, equal distribution, check the whites,

and that basically is all that is required at this point.

I always recommend that occasionally -- of course, you can't do it on compounded prescriptions that you get just occasionally because it wouldn't be financially feasible, but if a pharmacist is doing a product routinely, you know, every week, every couple of weeks, that they periodically take samples and send them all to a contract lab for analysis, of which many of them do. Many of your better ones do, like Dave was referring to awhile ago.

MR. TRISSEL: Apart from those issues, really a pivotal thing is -- I think we can all agree that to get a GMP manufactured product with GMP bulk, GMP manufacturing process in a suitable plant, a consistent product in the hands of all the patients who need it, would be a desirable situation.

The question only is really can that be delivered in terms of several thousand, maybe 5,000, maybe even more, patients. It would seem reasonable to give that a try and see if the company can deliver on their promise and we have a promise from you, right, that you will --

DR. COHEN: You have a commitment from us that we will do that.

MR. TRISSEL: -- for all patients whose physicians believed this would be of benefit.

DR. BEHRMAN: The answer to that is -- it would be impossible for any sponsor to address that because we would want to discuss the contents or negotiate the contents of the program with them. As Dr. Woodcock mentioned yesterday, second to the safety of the patients is the safety of the development program. If we believe that the expanded access program is going to make it impossible to develop the drug, we will put certain limits on that program. It is important to remember that there is not a right to access to drug in this country. That is nowhere in the law. It is done because -- it is done for a variety of reasons, but only when appropriate.

So, that means that it is always appropriate in the programs where the sky is the limit. I mean, when people think about expanded access, they think about some of the very large AIDS programs that we described for you yesterday, where, for example, 35,000 patients received 3TC. But that is not necessarily what is going to happen.

We may not determine that it is appropriate for every physician, who wants to get a patient on this program to do that. We may decide that we don't know enough about the safety. We don't have sufficient efficacy data or there is not sufficient drug supply.

So, again, you would have to trust us to negotiate a fair and appropriate program with the sponsor.

DR. COHEN: I think I will only add that in terms

of drug supply, from our point of view, we -- I will just repeat that we are capable, willing, able to supply certainly substantially more than the 5,000 number that you mentioned. If it were necessary and if it were agreeable and appropriate under the regs and in our negotiations and discussions with CDER.

DR. BEHRMAN: Because remember that any experimental drug carries with it -- well, any drug carries with it a risk, but particularly experimental drugs. We in that sense sort of try to stage the expanded access program so that the smaller ones are for the patients that have absolutely no options and clearly want to and are able and, if justified, tolerate the risk, as opposed to when we are much more confident that the drug, in fact, works and we are simply waiting for either the NDA to come to us or for us to finish the NDA, when a somewhat looser program is more appropriate.

MR. GRADY: I am Tim Grady. I am with the U.s. Pharmacopeia that has been mentioned here.

I missed the first 10, 15 minutes, so you may have covered this, in which case I apologize for the intrusion. The high variability is very suggestive of a vapor pressure problem. This was reported, for example, by Professor Ralph Shangra(?), the late, great Ralph Shangra, on nitroglycerine. So, the question I have with the compounded preparations,

were they labeled to be refrigerated? Were they delivered with a beyond use state? Or has anybody formulating this material as a salt? I mean, you have got a lot of electrons coming off of the neferadine(?) nitrogen and you have got amino group -- by the way, your amino purity is very easily -- you can bubble air into water with some of those molecules and make a nitroso compound.

So, very hot electron situation. So, the question is anybody making a salt out of these? So, I don't know that you can characterize the compounding situation for something with a high vapor pressure and I don't think the pharmacists should be beat up for the variability. It may well shop within the 10 percent that Dr. Allen is talking about, but a couple of warm days will take care of that.

MS. AXELRAD: I just wanted to clarify my earlier remarks about this and that is that the -- I was reminded that the statutory requirements that you comply with the compounding chapter and any USP monographs, if one exists, goes to the bulk drug substance. It does not go to the finished dosage form. So, there is nothing in the compounding law that actually specifically says that the finished dosage form, the actual compounded product has to comply with the USP standards.

DR. LIEBMAN: Loyd, I thought when we wrote monographs for compounded products, we said the finished

product has to be plus or minus. Jim, do I remember correctly, on compounded drugs? Jim, are you still here?

DR. JUHL: We can get clarification on that point because it is written down somewhere.

Let me ask one more question and then we will let you go.

Your distribution system, as you would see it, would be a centralized one or would you make use of pharmacists, who already have relationships with these patients, and attempt to take advantage of that?

DR. COHEN: We actually have been in discussions with a couple of contract research organizations, who -- one of whom in particular has specialized in managing and directing other expanded studies, particularly for some HIV compounds and some cancer compounds in the past, studies that have involved in some cases tens of thousands of patients.

So, our intent would be to contract with those organizations and follow their best recommendations as to how this would be distributed effectively. So, I cannot comment knowledgeably, personally, to you now about that, but I will tell you that we are --

DR. JUHL: You are not considering using the pharmacists that already have those patients?

DR. COHEN: Again, I don't know the answer to that question because this is not an area that I am expert in.

This is something that we will rely on the contract research organization to advise on and it may well be. We haven't had that specific conversation with them yet, but if they were to say, you know, an effective way to do this would be through these pharmacies that are already accessing these patients, that would be -- obviously, we would do that.

DR. BEHRMAN: It may be worth noting that that would be very atypical, because you have to have a physician to actually write the prescription or prescribe it. The interaction is between the physician and either the company or whoever is acting on their behalf.

DR. JUHL: I understand but, again, we are atypical because there are already patients on these drugs and how you are going to find them is the question.

Other questions?

[There was no response.]

We are running a bit behind schedule and I thank you. We will probably have some additional discussions after break, but I think we will take our break now and get to our next speakers on the diaminopyridine right after break.

Let's be prompt and be back in the room at five minutes after.

[Brief recess.]

DR. JUHL: Okay. We will resume.

Agenda Item: 3,4-diaminopyridine

We will now move to 3,4-diaminopyridine. We will then have an open public hearing where both compounds will be discussed and then the committee will deliberate on both compounds following that.

First, we have Dr. Donald Sanders from Duke University, who will talk to us on his experience of 3,4-diaminopyridine.

DR. SANDERS: Thank you.

I am going to be talking about the use of 3,4-diaminopyridine in neuromuscular diseases, predominantly Lambert-Eaton Myasthenic Syndrome. For the last 11 years, I have held an IND for 3,4-DAP, primarily to use it in Lambert-Eaton Syndrome. So, I am going to start with an introduction to that condition.

This is a very rare neuromuscular disease, affects probably fewer than a thousand, 1,500 people in the United States at any one time. The exact numbers are hard to come by because it is quite frequently undiagnosed or misdiagnosed.

It is a condition that affects muscle strength, begins typically with weakness of the legs, progresses to the arms. The clinical findings that lead us to the diagnosis are listed here. We find weakness in the hip and shoulder muscles. Tendon reflexes are reduced. Most patients have some evidence of autonomic dysfunction, particularly a dry mouth and occasionally they have weakness of the eyes or muscles

that control their chewing, swallowing or talking.

It results from an autoimmune attack against the voltage gated(?) calcium channels on the presynaptic motor nerve terminal. Actually, the condition affects many nerve connections in the peripheral nervous system, but the one that produces the weakness is diagrammed here. This is a neuromuscular junction, presynaptic nerve here, postsynaptic muscle membrane here. On the tips of the folded postsynaptic membrane are located the receptors, which receive the acetylcholine that is released from the nerve terminal.

In the Lambert-Eaton Myasthenic Syndrome, there are antibodies directed against the presynaptic voltage gated calcium channel. These antibodies block the release of the acetylcholine and that produces the weakness.

These antibodies act by cross-linking the voltage-gated calcium channel, which leads to their down regulation, reduction in numbers and there is also some evidence that the IgG, the antibodies, actually block calcium influx through the calcium channels.

About 50 percent of patients with Lambert-Eaton Syndrome have it as a paraneoplastic syndrome; that is, it results from an underlying cancer, usually a small cell lung cancer.

These are cancers that predominantly, if not exclusively affect smokers and, thus, if a patient with

Lambert-Eaton Syndrome is over age 50 and has a history of smoking, they almost undoubtedly have a small cell cancer.

In these patients with cancer, presumably these cancer cells, which are rich in voltage gated calcium channels induce antibodies that cross react with the nerve terminal voltage gated calcium channels. In the 50 percent who do not have an underlying cancer, then, presumably, this disease is a part of a more general autoimmune state.

These are the ways that we go about treating Lambert-Eaton Syndrome once it is diagnosed. The first thing we do is to look for an underlying cancer and treat it if it is found. Many patients will -- if they are successfully treated for cancer, will have improvement if not resolution of their weakness and, thus, sometimes don't need any further treatment.

However, the majority of patients do need treatment. This is a disease that produces variable degrees of debility. Most patients have moderate to moderately severe dysfunction, which means they are able to carry out their activities of daily living, but not their normal activities. Rarely, the disease produces such severe weakness as to be life threatening.

We begin treatment by seeing if they will respond a cholinesterase inhibitor. Mestinon is the one that we use most frequently. It doesn't usually do very much, but occasionally some patients will get benefit, particularly

in some of their autonomic symptoms.

Based on our experience and the experience of others throughout this country and throughout the world, we considered 3,4-diaminopyridine to be the next treatment of choice, if it is available. If it is not available, then guanidine, which is an agent that has been used for many years to treat Lambert-Eaton Syndrome is sometimes used. It has a very high toxicity profile, however, and most people who have used it, including the patients who have used it, would prefer not to.

We do consider the use of various forms of immunosuppression in these patients, depending upon the severity of their disease and how well they respond to 3,4-diaminopyridine. Things that have been used with variable success include high doses of steroids, such as prednisone, other immunosuppressants, such as azathioprine(?) or cyclosporin, plasma exchange or high doses of IV Ig also can produce significant, though temporary, improvement.

In these patients, even if we don't find a cancer initially, we frequently and periodically reassess for the presence of cancer, which may not have been detected initially.

3,4-diaminopyridine has been used in the treatment of Lambert-Eaton Syndrome now for -- I can't see the date -- is that 1984? Okay. That was the first report of its

use in Sweden. The reports were so enthusiastic that whenever or wherever it could be obtained, it rapidly became the treatment of choice everywhere in the world, except in this country, where it has not been available, other than on protocol.

3,4-DAP, like 4-AP, blocks the voltage gate, voltage dependent fast potassium channels in their closed state, which prolongs the falling phase of action potentials throughout the nervous system, which then enhances the calcium entry into the nerve terminals, which then enhances transmitter release.

These are some slides made from studies we did more than 20 years ago on 4-AP in action potentials from normal and myasthenic patient muscles, just to show what it does to an action potential. This is a normal muscle action potential and this is its prolonged form after having been exposed a low concentration of 4-AP. This is what 4-AP does to Lambert-Eaton Myasthenic Syndrome neuromuscular junctions. We infer that 3,4-DAP, which has a very similar mechanism, does the same thing.

Here on the top we see in plate potentials recorded from the post-synaptic muscle, initially in a controlled solution and then at various times after 4-AP is introduced into the solution, showing the enhancement of the amplitude. Here at the bottom is just a longer term diagram of the same thing. The amplitude increases and ultimately becomes normal

and effective in producing muscle activation.

This is a slide from that initial report from Hoken(?) Lund(?) and his co-workers from Lund, Sweden, showing what happens to the muscle respond that is elicited by a nerve stimulation in a patient with Lambert-Eaton Syndrome, after administration of initially -- this is diaminopyridine by itself and this is diaminopyridine with an acetylcholinesterase inhibitor at the same time, showing that the action of these two works -- the actions of these two are synergistic and much more than either alone.

There has been one controlled study of DAP published to date. This is a study by Katy McEvoy and Tony Windebank and others from Mayo Clinic, which was published in the late eighties. This was a small series of patients, but the benefit both in terms of their function, the electromyographic muscle recordings and autonomic symptom improvement in patients receiving it for Lambert-Eaton Myasthenic Syndrome.

We have been using it since 1988 for this purpose and to date have treated 53 patients with LEMS. We have had a couple of blinded studies, the most recent of which has just been completed under sponsorship of the orphan products program and the results of which, although we know what they are, I haven't got the data to actually show you the numbers. But this is a summary of the clinical response in these 53 LEMS patients that we have treated so far.

Forty-five percent had a marked improvement. By that, we mean they achieved relatively normal functions of activities of their daily living. Thirty-four percent had moderate improvement, which means a significant improvement in their lifestyle and a smaller percent had either minimal improvement that was not enough to justify continuing its administration and a very small number had no response to DAP at all.

The obvious conclusion here is that in this disease for which there is no other really good treatment, the overwhelming majority gets significant benefit from DAP.

This is a slide for a press release -- you can use this if you like -- showing a patient with Lambert-Eaton Syndrome before and after she received a single dose of 15 milligrams. Here she could not lift her arms over her head and here she was brightly smiling and reaching for the sky. She was delighted when I told her I was coming here and I was going to show her picture. She is one of our enthusiastic customers.

These are some measurements from the most recent study that we have completed. We did a study that involved the treatment of 26 Lambert-Eaton Syndrome patients. It took us five years to accumulate these, but these are the data using as a measurement of efficacy a quantitative function score, which involves timed measurements of the function of various muscle groups in the body that is then summated.

We see that the scores in the patients who receive placebos -- this is the change in their QMG score from a baseline -- is really no different from the baseline value here; whereas, after the administration of 20 milligrams DAP three times a day for five to six days, their QMG scores had significantly fallen.

This just shows the change in QMG score amongst these patients, comparing those who had received placebo, virtually all of whom had very little or no improvement in their QMG score versus the patients who had received diaminopyridine, showing that there was a variable change in this score, but virtually all patients had significant improvement.

Similar observations on the muscle measurements that are used to quantitate the severity in this condition, the compound muscle action potential, which is the size of the electrical response you elicit from a given muscle when you stimulate its nerve. Here on the left, the placebo group showed no change from their baseline values after five to six days; whereas, the amplitude of this muscle response was significantly higher in the patients who had received blinded diaminopyridine.

This study involved an initial blinded phase and a subsequent open label phase during which we optimized the dose to determine the best dose response in individual patients.

These are the ultimate doses that we determined to be optimal in the 24 patients, who ended up taking open label drug.

The dose was sometimes as low as 20 to 30 milligrams a day, but occasional patients took doses up to 80 or even a hundred milligrams a day to achieve their optimal benefits. So, there is a variable dose requirement in this condition among patients.

After determining the optimal dose in patients, we then added Mestinon to it to see if that would make them better or if not, would allow us to reduce the dose of DAP to a lower level in order to avoid side effects.

Patients require anywhere from 5 to 25 milligrams per dose in order to achieve their maximum benefit. It is administered every three to four hours during waking hours and in almost all patients, the addition of pyridostigmine, Mestinon, at a dose of 30 to 60 milligrams, three or four times a day, significantly prolongs the duration of action of the medication and/or increases its maximum response.

The side effects are usually trivial. Perioral and digital paresthesias are reported by most patients, who take doses higher than 10 milligrams, these paresthesias occur usually 10, 15 minutes after the patients take a dose and are rarely unpleasant. In fact, I have some patients who tell me that it is actually a nice little buzz.

If the dose is taken late in the day, it has produced

insomnia in some patients. Seizures are a problem if high doses are used. When it was initially introduced or described in Europe, doses of a hundred milligrams a day were the recommended standard and that is doses that we used initially in our protocol as well and the Mayo Clinic protocol used that dose as well.

On that dose, there have now been to my knowledge three patients who have had seizures. One of our patients did. We don't use those doses now, primarily because we have found with experience that by using cholinesterase inhibitors along with DAP, we don't need to use such high doses to get the optimal benefit. But it is necessary to titrate the dose in each patient individually in order to determine that.

Since DAP and cholinesterase inhibitors do have synergistic actions, the DAP can enhance cholinergic symptoms in these patients, cramping, diarrhea, that sort of thing, nothing really of major concern.

I am sorry you can't see this slide. I can't either. But it is just to remind me of some of the symptoms that we queried the patients about in this blinded study that we performed and it really showed that there was no -- the only symptoms that were significantly more frequent in patients receiving drug compared with placebo were related to the paresthesias that they had.

In conclusion or at least in summary of our experience,

we found that 85 percent of patients with Lambert-Eaton Syndrome obtained significant clinical benefit from DAP with no significant side effects at the usual clinical doses. The benefit is complemented by Mestinon and at least at the present time it is available only on protocol or for compassionate use.

We initially obtained diaminopyridine as a purified commercial product from a commercial chemical company, but about five to six years ago, Jacobus Pharmaceutical took it on as an orphan product and has been providing it for us at no cost since then. They have recently developed a pill formulation. Initially, we obtained it as a purified powder. Our pharmacy mixed it up in capsules for us, but now we are getting it in pill form. It does have to be kept refrigerated in order to maintain its integrity.

We keep it frozen in our laboratory and send it out in refrigerated containers to patients who are receiving it. This works as long as Jacobus continues to provide it for us and we can continue to afford to pay the postage for the patients. We haven't yet figured out a way in which the patients themselves can pay for this.

The way we begin it usually is to have the patients taking 10 milligrams three times a day for two weeks and observe the response. We then increase the dose by 5 milligram increments until we have determined its maximum effectiveness

based on primarily the patient's symptoms, not to exceed 80 milligrams a day.

After we have done this, we add Mestinon in graded doses to reassess the maximum effective dose and it is necessary to periodically reassess the optimum dose in these patients because the disease changes over time. We have had some patients who have had spontaneous improvement and don't need as high doses as they previously did. And we would never know that unless we had this periodic reassessment. So, that is built into our protocol.

There has been some concern about cardiac toxicity, theoretical concern, based primarily, I think, on what it does in experimental animals at high doses. To my knowledge, there has not been any report in the literature of any such effects on patients and we have not had any. But to examine the effect on the heart rhythm in the study that we did, we looked at the corrected QT interval, the QT interval and the corrected QT interval and EKGs in the patients on DAP and on placebo and this is just to show that if anything the patients who receive blinded DAP had less of a change in their corrected QT interval than the patients who were receiving placebo. But there is no difference and we don't feel that there is any significant cardiac toxicity at the doses that we are using or likely to use.

What has been the response in our experience to

the other treatments? A very confusing graph, I think. Probably this table, if you can see that, is more informative. We did a retrospective study or evaluation to see how well other forms of therapy had benefited the patients that we have seen.

We compared those with the benefit from diaminopyridine and I think if you just follow the top two lines over here, you will see that percentagewise none of the other treatments even comes close to the benefit that patients obtain from diaminopyridine.

So, in conclusion, in treating patients with Lambert-Eaton Syndrome, we always go after any underlying cancer because occasionally treating that can produce marked, sustained benefit. Pyridostigmine, Mestinon, by itself is usually ineffective. Diaminopyridine is usually beneficial and even more so when used with pyridostigmine. Plasma exchange and high dose immune globulin frequently give marked, though, temporary improvement in these patients.

I don't consider these forms of therapy to be viable, long term therapies in patients because of logistics and expense, but, occasionally, they are necessary. Other forms of immunosuppression produce variable degrees of benefit in some patients, but rarely gives marked benefit and in my experience has never given patients as much benefit as they get from diaminopyridine.

I want to take just a couple of minutes to present a couple of cases to exemplify how we use it and how it has worked. This patient had the autoimmune form, non-cancerous form of Lambert-Eaton Syndrome, which began when she was 39 with proximal leg weakness, which progressed over several months to involve her upper extremity muscles. She also had some mild weakness of her eyes and bulbar muscles.

The diagnosis was made by electrophysiologic testing and no malignancy was found. She was initially begun on Mestinon, which produced some mild improvement and then she was begun on asathioprine, an immunosuppressant. Didn't really do very much. She had three treatments with plasma exchange, each of which produced dramatic but transient improvement.

She also received five treatments with IV Ig, which, again, produced some transient improvement. Steroids was given in high doses, which produced what was referred to as good improvement, but she developed a vascular femoral head necrosis, a recognized complication of prolonged steroid administration. She joined our protocol early on. She achieved dramatic sustained improvement with diaminopyridine. Her optimal dose was 10 milligrams every three hours with 120 milligrams of Mestinon every three hours.

She has now been on DAP for, I think, six or seven years and you would be hard put to get it away from her.

This is a patient who has the paraneoplastic form of Lambert-Eaton Syndrome. He was a smoker. At age 39, he began to have trouble with skiing and progressive fatigue, proximal muscle weakness over the ensuing months and the diagnosis was made seven months after onset. His cancer was not found on the initial screening, despite the fact that very vigorous screening was done. He was treated with Mestinon with no benefit. Prednisone produced slight benefit. Guanidine produced increased endurance and strength, but he had lots of side effects from it that were unpleasant and he joined our protocol in 1992.

He had a dramatic improvement with 20 milligrams, three times a day. He was able to walk. He actually went back to work. Unfortunately, about a year and a half later, he developed brain metastases, which were the first manifestations of his lung cancer. Seizures came along with that. So, we had to stop his DAP and when we stopped his DAP, he became bedridden. He died several months later of the results of his cancer, but after his death, he wife wrote me a very poignant letter in which she said he wanted me to tell you this, that you had given him two years of useful strength because of the DAP.

Thank you.

DR. JUHL: Thank you, Dr. Sanders.

Questions? Dr. Gilman.

DR. GILMAN: When I looked through this material and then hearing the commentary this morning, I was rather unimpressed with the beneficial effects in multiple sclerosis of this agent, of 4-AP, but very impressed with the benefits of DAP in Lambert-Eaton Syndrome. I also called colleagues at the Mayo Clinic, the people who had done the initial trial in 1989 with Lambert-Eaton Syndrome.

They have about 30 patients ongoing that they are treating and I would say their e-mail message reflected your experience, that it is very effective and that it is very safe. So, I didn't get any quantitative statements from these people and I wanted to ask Dr. Sanders. So, you go up to a maximum of 80 milligrams per day. What is the prevalence of seizures on that dose?

DR. SANDERS: I don't know of anyone who has had seizures on that dose, other than patients, such as the one that I just presented, who had brain metastases. He had demonstrated brain disease, which is probably the cause of his seizures.

DR. GILMAN: Do you get seizures with any lower dose?

DR. SANDERS: I have never heard of anyone getting seizures at a lower dose, other than those circumstances.

DR. GILMAN: Do you monitor the blood levels in these patients?

DR. SANDERS: No, we don't. We have not found that the dosage that we use produced blood levels that are detectible using the techniques that we have had available to us.

DR. GILMAN: Do you have any evidence suggesting that different compounding pharmacies produce different concentrations or highly variable responses in your patients?

DR. SANDERS: We have only obtained the DAP from the sources that I indicated. I wouldn't have any way of knowing whether a compounding pharmacy would be able to produce the drug at the concentrations and with the reliability that we have been achieving it.

DR. MC BURNEY: Dr. Sanders, as I understand, you have had no difficulty in obtaining the drug when a patient needed it?

DR. SANDERS: No difficulty in obtaining the drug -- well, it is a complicated process. It is a three-way -- you know, it is a three ring circus. We get the drug from Jacobus Pharmaceutical. We store it. We send it out to the patients when they need it. They resupply us. I wouldn't say we have no difficulty, but we have had no patients who have failed to receive it.

DR. MC BURNEY: So, there has been availability.

DR. SANDERS: There is availability but there are problems with the availability, as I mentioned before.

DR. RODRIGUEZ: You mentioned that things have --

the medication has to be kept frozen or refrigerated and the question that I have is realizing the realities of human beings, what is the stability, for example, at room temperature? Would it last 24 hours, 6 hours, 8 hours, 10 hours? You are giving it three times a day and that means that people will have to have access to a refrigerator three times a day. I was just sitting over here thinking as somebody who takes medications regularly, what is the -- would six hours be -- still give you the same amount of strength or potency that you wanted?

DR. SANDERS: I am going to defer any questions like that to someone who knows a lot more about that issue than I do. We keep it frozen in the laboratory until we dispense it out of just precaution. Whether it makes that much difference that it is refrigerated or not, I don't know. We haven't done the sort of studies necessary to demonstrate that.

Considering the inherent unreliability of patients in taking medications the way they are prescribed, I think that if it were really a problem, we would have heard about it from some of our patients. I am sure they leave it unrefrigerated from time to time.

MR. TRISSEL: If I understood you correctly, your initial cadre of patients were treated with pharmacy compounded capsules from raw material.

DR. SANDERS: That is correct. Through our research pharmacy at Duke University.

MR. TRISSEL: And there were successes then, I gather, using that material to lead you to believe that this was a successful product?

DR. SANDERS: Yes.

MR. TRISSEL: I notice that the distribution of patients enrolled on trials is non-uniform in the United States to say the least. That looks like North Carolina and Minnesota have the lion's share of the patients and I can't believe that the patient distribution is really like this.

DR. SANDERS: The patient does go where the drug is, sir. Our patients come from all over the United States.

MR. TRISSEL: They do?

DR. SANDERS: Yes. We turn them into Blue Devils when they get there.

DR. JUHL: This is location of the physician, not necessarily where the patients are from.

DR. SANDERS: Exactly.

I didn't mention the potential value of this medication in other neuromuscular diseases, but we and others have also used it in occasional patients with congenital myasthenia gravis, which is a very rare group of conditions for which there are few good therapies. We have had good results in some of these patients. So, that is another

indication for this medication.

DR. KATZ: I just want to reiterate one caveat about the warrant of safety at lower doses with this or any drug, but here specifically. Even if it were the case that we had complete follow-up or complete knowledge of patients experiences at doses lower than a hundred -- and maybe we do have complete follow-up, I don't know -- the number of people who have been exposed to any dose, let alone a dose lower than a hundred, is pretty small, I think. I don't know what the totals are, but I think in the Mayo Clinic -- well, we have the numbers here. Okay. So, it is not that much.

So, even if you had not seen any seizures if they had a lower dose, the warrant that -- the risk that you can cap with that experience is fairly high. So, it is possible it could -- we know the drug or at least we believe the drug is capable as a molecule of causing seizures. It is certainly -- given the variability in the population, it is possible that it could cause seizures at a lower dose of -- and you can figure out what percent and you still wouldn't have seen any in this very small cohort of patients who have been exposed. So, it is just something to consider.

DR. SANDERS: We have been in contact with the groups around the world, who have had extensive experience with this. Dr. Lund now has treated patients for -- well, since before he published his first report in 1984 and the Mayo group,

as you mentioned, have treated about 30 patients. So, probably the world's -- these three groups probably represent most of the world's experience with it and none of these folks, to my knowledge, have seen seizures at a dose less than a hundred milligrams a day.

The availability or entry of DAP into the central nervous system is much lower than 4-AP, as you know, and that is its main advantage in treating patients with peripheral nervous system diseases.

DR. JUHL: Thank you very much, Dr. Sanders.

Our next speaker is Dr. Jacobus, who is president of Jacobus Pharmaceuticals.

DR. JACOBUS: Mr. Chairman, the slide projectionist is Laura Jacobus. I am Dave Jacobus and I do work in the Jacobus Pharmaceutical Company. And we are a small company that actually makes the active ingredient and then makes the dosage form and then does the appropriate registration and distribution and so on.

We synthesize the active ingredient, 3,4-diaminopyridine, in addition to making the dosage form. Now, this first slide is the slide to which I think Dr. Sanders responded. There is a huge concentration of patients there. The Mayo Clinic, Katy McEvoy, Tony Windebank, and this is Constance Bowe, B-o-w-e, a pediatric neurologist, and she has patients from this part of the country all the way over

to here.

She has been a very active investigator and has done preclinical work as well. Now, for this committee, this committee should understand how these patients got on this chart because these don't represent pharmacy dispensing patients because we don't have a record of them. These are the patients in our roles and these are all physician-sponsored, investigational, new drug applications.

For the major centers, such as Don Sanders center, he has his own IND and the study goes along and it is well-established. But what happens when an investigator from an isolated state has an emergency, has a patient in whom the diagnosis is made. They call us or we get a call relatively soon and we send -- for those of you who are not in either the Agency or maybe in industry, it is nice to hear how this system works.

We send a package of information to them so they can get an investigator-sponsored IND. We help them with the forms, but they have to write the letter. They send it to the Division of Neuropharm. The consumer safety officer, Teresa Wheelis(?), is very effective and if it is an urgent situation, the Agency will take the equivalent of a "Dear Doctor" letter, thank you for sending us this interesting patient, you know, the kind of thing that you do all the time, will take that thing, take the forms by fax, provide an IND

number on the telephone. That physician calls us back and we can have the medication there by the following morning.

That is how -- now, for others, the medication is stored, you know. Supplies are sent to the Mayo Clinic in Rochester and to Connie, but for others, who have these isolated ones, it happens very quickly. Actually, that is one of the nice things that is nice here to say. The physicians who call are good physicians. They truly are interested in getting something for their patient that won't happen otherwise, but the Agency, whoever understood publicly that the Agency routinely supplies an IND number on an emergency basis like that. That is not the public perception. It is very nice.

Now, the next slide demonstrates the chemical structure -- and you would expect since we make it we would show it -- 4-aminopyridine is right -- 4 because it is right opposite here, 3,4-diaminopyridine is here. It is unstable. We do ship it cold. The patient doesn't have to carry a refrigerator around with him. The tablets will last a month or so at normal temperature, but not in distribution conditions. That was a good question.

Now, I would like to show the next slide. We have proposed and we proposed kind of before -- we had this system going for another drug in which we gave -- we give away another drug that was not available and now we had -- after having supplied Dr. Sanders and the Mayo Clinic, we thought that

we needed to make a commitment to bring the drug to market so that it would be available so that we could put labeling in the PDR, so people would know how to handle it. Therefore, to handle these, we also thought perhaps with all of these isolated INDs roaring in, that it might be helpful to the Agency -- it would certainly be helpful to us to be able to collect all the information and to assembly the safety records, such as it is.

So, we have proposed to the Agency, and the Agency has not had time to respond, a compassionate Phase 3 distribution program, which I am going to outline to you. We do have an IND and we are suggesting this be extended under our existing IND and there is amongst other things, the patients would be covered if -- more easily, perhaps, than a physician filing their own IND.

Then there is an informed consent, which everybody agrees to and we presented it to the Duke IRB. We wished to present it to the Duke IRB because Duke has Don Sanders on their staff and, therefore, they will have a faculty member, who will really be knowledgeable about the risks and benefits.

Then we have a desire to really collect and be sure. It is a convulsant. We think you need to know an EEG. You need to know a basic electrocardiogram. We have developed suggestions of the reasons why an IND is going to help the progress of the drug come forward.

But to make it easy, we thought that we could do most of the initial stuff on the phone. We need the physician. We need all of the information on the patient because when we distribute the drug, the patient's name is on the bottle, as well as the physician's full name and address. We register the patient and we expect to receive that same "Dear Doctor" letter that the Agency receives, along with the latest laboratory information or an agreement to collect this information when the patient first comes back to the office.

On the next slide, we have written the entry criteria and I have sent the slides to Don and I have hopes that it is reasonably right, but we do expect -- the big thing in a compassionate distribution program, I think, is to make sure -- it is true in any study -- make sure that the patient who gets into the study has the disease you are wanting to study. We do really insist on that here and in the next slide you will see the pediatric.

We think it is appropriate. The management of the drug is perhaps different in the pediatric patients, but there are patients in Connie Bowe's place who if there is an hour delay in not taking the drug, then the symptoms will again appear. These, she believes, are the entry criteria that she should have for pediatric patients, but we believe that in standard practice these days, pediatric patients should be included.

Now, this is really -- these inclusion and exclusion slides are standard parts of the protocol. They are parts for our existing protocol, which was primarily dovetailed into Duke. This is what we are expecting to apply broadly and we are planning, however, to put the drug always on top of pyridostigmine.

The next slide shows this exclusion criteria and the next slide. We have rules for this compassionate thing, based on our existing things. We ask that the physician -- if we have to do this fast emergency distribution, there won't be time to get an informed consent because you will shift the medicine and the patient may not be in the office then and so on. So, we ask that the physician start the product only after having had the informed consent signed and in this case obtained the basic entry data.

The tablets are designated only for that patient in a system analogous to the named patient system in the United Kingdom. If that physician has another patient, then that new patient requires another registration. We do receive requests to send sometimes tablets to the patients, but the tablets are sent to the physician's office. There are an occasional -- there are enormous distances in the Midwest sometimes. North Dakota, you can be a thousand miles away from the patient under your care. But we then act as the physician's -- we do that only with established physicians

and we act with their -- as their shipping agent.

After one month in this study if the informed consent has not been received back from us and if the patient has not been benefited or the laboratory data is not up to speed, that patient is out. We have one difference here, which was shown in Dr. Sanders' slide. The proof of continuing benefit, 3,4-diaminopyridine is unusual, very unusual amongst medications. There is no fundamental benefit to it. Maybe helping breathe is an important thing. Improved muscle power is important. There is nothing on the underlying effect of the disease progress.

One can stop the medication and all of the symptoms will immediately return. Start it again and they will immediately go back to where you were before. And this forever and forever, for years and years.

We have proposed -- we had said in our first IND and we have said in our compassionate application, that we think that the proof of continuing benefit is something that actually should flow through to the labeling. That is to say, periodically the patient should be retitrated or perhaps one should take advantage of accidental compliance problems. Went to visit his son at graduation and forgot to take something or missed out on a dose and -- or if there has been no evidence of an accidental non-compliance, then our protocol will require a dose delay, a dose reduction or a dose vacation.

We think by that there will not be a tendency amongst patients to -- that will teach the patient, yes, the medicine is good. That will teach the physician it is good. It will also teach them the opposite. If they don't need it, they don't need to take it.

We have made a very simple scale, a global response. We have pediatric endpoints, which are equally easy to obtain.

Lastly, we think it appropriate because there is a rumor, you know, how can you get 3,4-DAP sometimes. We think it appropriate and we have done it before in the past in other programs, that we let the attending physicians who are liable to receive these patients know of the availability of the compassionate IND. So, when that is approved and when we are set to go, we will do it.

Thank you.

DR. JUHL: Questions. Elizabeth.

DR. MC BURNEY: Actually, I have a comment to make and I want to on behalf of patients that have another disease, called dermatitis herpetiformis. Dr. Jacobus's company has made available at no charge another drug called sulfapyridine and this program has been in effect for a number of years. I have had some patients participate in it now that I know for at least six or seven years. So that there is a track record here of this type of program working and working very

successfully.

I think that should be taken into consideration and I wish to thank you for that.

DR. JACOBUS: Thank you.

DR. JUHL: Questions of the committee? Sir?

DR. SANDERS: I would just like to make a comment about a question that was addressed to me and perhaps I didn't answer it entirely. It had to do with any problems that arose during compounding of the drug before Jacobus began making it as a pill.

It was packaged in capsules by our research pharmacy and during the seven or eight years we used that, we would quite frequently get calls from patients after they had received a supply of the medication asking if we had changed it because they thought it wasn't working as well as it did before or they would tell us, well, you know, you get a super capsule every now and then and some of them are just duds.

We had no way of knowing whether that was true or not. We would have them bring their capsules in. We would analyze it to see if there was any variability. We never convinced ourselves that there was. Whether that is a problem in the compounding or whether that is placebo effect, I have no way of knowing, but I can tell you that if it is put up in a pill, that is not a question.

DR. GILMAN: I would just like to know whether the

company will continue to make this drug available if it is put on the list of drugs that can be compounded?

DR. JACOBUS: We have made it available for nine years or I think nine -- we were trying to discuss, eight or nine years and as far as I know, compounding is possible now and I see no reason -- I think I am neutral on this issue. I think that pharmacy is a very important branch of us and we have pharmacists in our employment. We all depend on pharmacists for dispensing. They are part of the system. I think it is a more difficult thing to do and I think that there is a lot of things pharmacies can do.

I am not sure whether pharmacies want to handle things like this but I think that the advantage of making a systematic way of handling it -- I am neutral on it. I am not an expert in that. I hear the thing -- we will continue to answer your question. We think that we have to collect the data. We think we have an obligation to make it available. We have had our troubles with supplies and manufacturing and all the rest of it.

There is a lot more commitment of the Agency than when you market it, you know. They will need tons of extra data and the district office visits and -- it is a true commitment. We will bring it forward.

DR. JUHL: I would like to echo Dr. McBurney's comment. It is a pleasure to see a good patient oriented

system that has been under operation for a long time. It gives us reassurance.

Help me understand the entrance criteria that you have outlined. Amongst neurologists in the area, are these criteria sufficient to distinguish between patients who have the syndrome and those that don't? Or are you looking for a more severe group of patients with which to collect data?

What I am wondering, are there people who wouldn't make it in to your protocol because of the level of the entry criteria?

DR. JACOBUS: I personally think the answer is "no," but Dr. Sanders is here and his answer ought to prevail.

DR. SANDERS: There might be rare patients who don't meet those entry criteria, but these criteria were actually based on our experience in analyzing these factors amongst the patients that we have diagnosed with Lambert-Eaton Syndrome. But since it is such a rare condition, there may well be patients who have an unusual form or a very mild form of it. One could then ask whether they would really need this therapy at that point.

I don't know whether those criteria are open to discussion on an individual basis or not. I would think perhaps so. A lot depends upon the experience of the physician in dealing with this disease. There are not many people who see lots of these patients because there are not many of them

out there.

DR. JUHL: Few have your level of experience. I am just wondering how many arguments you get into over the criteria at meetings when --

DR. SANDERS: I can certainly envisage a scenario where someone would call me up and say, listen, I have got a patient. I know he has got LEMS because he has got lung cancer and this, that and the other, but he just doesn't happen to make 50 percent facilitation. I would say he has got LEMS. But I don't know whether Jacobus will be able to make that --

DR. JUHL: Thank you.

Any other questions -- oh, I am sorry. Go ahead, Dr. Jacobus.

DR. JACOBUS: Let me add to that that there is built into the trial the patient itself having -- patient having an opportunity to stop and start. It is built into the informed consent. It is designed -- we originally had a double blind, but not in the compassionate one, so that I think if you have that in as a safety device, then you can allow patients in and see what happens.

So, I think that if a -- I think in our other trial, we have with sulfapyridine, we had originally limited it just to dermatitis herpetiformis, but then there are other conditions that dermatologists use the medication for and

we referred those to the Agency and then the Agency said please broaden those things so that we don't have to get all these calls.

I think, actually, with a built-in device, one would tend to allow a trial to see if there was a benefit or not because that is part also of determining the limits of where it works or it doesn't work in writing effective labeling.

MR. TRISSEL: I was glad to hear that it doesn't sound like the cost of the drug would be an issue for patients. It does sound like the cost of transportation to a site might be an issue for patients, who don't have the personal resources to afford that. Am I correct in that?

DR. JACOBUS: It has been more of a problem for Dr. Sanders than it probably would be under the compassionate IND because we send stuff in a little cooler, like you kind of see at a baseball game. Then we send a call tag the next day to pick the cooler up. So, both of those transports are borne by us. What we say in the informed consent, this draft informed consent, that the Agency has yet to see, is that the patient or the physician or the service or whatever has to bear the cost of the laboRatory. We will not cover that in any way.

MR. TRISSEL: So, for patients who have Medicaid or something like that, they are not really eligible for this? There is no funding for somebody in Nebraska to come to Duke

to be put on this program and then --

DR. JACOBUS: That is true, but on the other hand, there is no funding from a compounding situation either.

MR. TRISSEL: Well, there are charity hospitals that do provide indigent care.

DR. JACOBUS: Then fine with us. Let them provide it.

MS. JACOBUS: We provide the drug free of charge and the hospital in which the neurologist is affiliated foots the bill. So, it is an indigent program because we don't have a -- we don't charge anything for our compound or the shipping on that.

MR. TRISSEL: Right. And that is different than the previous compound, which the patients have to pay for presumably out of their own pocket.

MS. JACOBUS: I don't know about that.

DR. JUHL: So we don't get confused now, the expanded access that you are proposing would have expanded numbers of investigators so they wouldn't need to come to Duke or to Mayo or they would need to come to Duke or to Mayo?

DR. JACOBUS: They would not come to the main centers to date. The main centers to date have been after us to get the program forward and I have told Dr. Sanders that I think he is actually been instrumental in bringing the drug to a point where we know enough about it that, in fact, it can

be considered for development.

DR. JUHL: Good.

DR. SANDERS: Could I just make one point? I want to pick up on the comment made about the hospitals bearing the cost of this. My hospital doesn't bear the cost of this and I don't know that there should be any official expectation that any hospital should take up these costs. These are societal costs.

DR. JUHL: Other questions?

[There was no response.]

Let me first of all apologize for getting us behind. We are. We should have had the open public hearing at 3:15 and we are almost an hour behind and I apologize both to the committee and especially to our participants in the open public hearing for making you wait.

Let us go to that portion of the program now.

Agenda Item: Open Public Hearing

We have four guests, who will address us on various topics related to the use of compounds. I would ask that each of our guests identify themselves, who they are representing and whether or not they have ties with any of the commercial ventures with whom we have had discussions this afternoon.

First off is Thomas Mick Countee(?), Jr., executive director of the National Spinal Cord Injury Association.

Mick.

MR. COUNTEE: Good afternoon, Dr. Juhl and other members of the committee.

My name is Thomas H. Countee, Jr. I am the executive director and CEO of the National Spinal Cord Injury Association, which is based on Silver Spring.

The National Spinal Cord Injury Association is a 51 year old organization, non-profit organization, with 45 local chapters and support groups from Maine to California. It is the nation's oldest and largest civilian organization dedicated to helping people with spinal cord injury and disease.

On a personal note, let me tell you that in 1958, as a result of a dive in the Chesapeake Bay, following my sophomore year at Harvard, I suffered a compression fracture at C-5,6 and that rendered me a quadraplegic. At that time, of course, there was no talk about a cure or a therapy for a chronic or traumatic spinal core injury.

You asked me to state whether the organization has any ties to the pharmaceutical companies. Among our corporate sponsors is Elan Corporation. Our corporate sponsors also include Medtronics, Neural Control, State Farm, AS(?) Mutual, a number of other corporate organizations.

Let me go on to say that the main reason I am here today is because the National Spinal Cord Injury Association is, among other things, interested in the health, safety and

welfare of our 5,000 members and the more than 250,000 persons with spinal cord injury and disease in the United States. That is our primary interest, not the economic or profit-making interests of any company that is making 4-AP or other therapies associated with spinal cord injury.

The primary mission of the National Spinal Cord Injury Association is to work to empower individuals with spinal cord injury and disease, their families, their caregivers, to make informed choices and to take actions to achieve their highest level of independence and personal fulfillment.

The association accomplishes our mission by three main strategies. The first is to promote, encourage and, where appropriate, fund basic research in central nervous system tissue regeneration. We do that out of three modest restricted research funds and have done so for a number of years.

The second objective is to collect and disseminate information and research relevant to the health, safety and well-being of our members. In that regard, we maintain a Web site, spinalcord.org, that provides comprehensive coverage of news affecting people with spinal cord injury and disease.

News coverage is broadly-based and addresses a variety of vital issues ranging from political events, the legal/bioethical issues, the medical breakthroughs. In

addition, our Web site provides up-to-date information on spinal cord injury and disease, national and local events and services.

Finally, the association provides its members with a quarterly publication, SCI Life, that serves as a repository of information and a forum for the concerns of people with spinal cord injury and disease.

Thirdly, we have, as I said before, about 45 chapters across the country. These chapters provide peer counseling, hospital visitation, spinal cord injury prevention programs in the national population through direct contact with persons who have spinal cord injury or disease, their families and caregivers.

We support the local chapters and we are available to advise them on various political, financial and medically oriented issues. Based on the National Spinal Cord Injury Association commitment to our mission, I would now like to address the issue of the compounded formulation of fampridine or 4-AP.

I would encourage FDA to restrict the availability of this formulation because of the potential negative side effect profile that has been discussed at great length. It is understandable that people with spinal cord injury has been experimenting with and actively obtaining this compound as fampridine has properties that appear to enhance local

function, positively affect spasticity, increase sensory function, improve bowel, bladder and sexual function.

These are reasons that such a large number of patients are seeking the drug. Given this drug's potential to enhance quality of life for persons with spinal cord injury, the joint efforts of Acorda and Elan to successfully market a stable, sustained release compound in compliance with FDA regulations with indications for treating SCI and multiple sclerosis should be fully supported.

Finally, the National Spinal Cord Injury Association believes that the Acorda plan for expanded access should be encouraged by the association and we do so here.

Before I close, let me give you another personal note. In my former life, I was an attorney with Securities and Exchange Commission, Division of Trading and Markets and also the Controller of the Currency. So, I am very well aware of the competing interests of a regulatory agency, industry, consumer advocacy groups, et cetera. I am very sensitive, as I have sat in the place of FDA a number of times in my role at the Controller of the Currency at the Securities and Exchange Commission.

I was also at one time legislative counsel in the White House and as fate would have it, FDA was one of the agencies under my responsibility from the Executive Branch side of the government. I am also the parent of a daughter

with bipolar disorder with schizoid aspects. She takes a drug that many of you are probably familiar with, viprexa(?).

As a parent of a child with a psychiatric disorder, I follow everything that I can on the development of various medications and therapies to deal with the disorder that my daughter has. So, if I sound somewhat passionate about this issue, perhaps you will understand, based on my personal and professional background.

I would request respectfully that you allow Acorda Therapeutics to grandfather in the individuals, who are receiving the compounded drug, to participate in the ongoing clinical trials that Acorda is conducting. Coincidentally, last night in New York in a totally different setting, I had the opportunity to discuss this issue and this upcoming hearing with Donald Ganey(?), the chairman and CEO of Elan and Thomas Mensch(?), the chief financial officer of Elan.

I put the question to them whether or not they were willing to commit resources behind an expanded access study if the compounding -- if the fampridine was not put on the compounding list. They assured me that Elan was prepared to commit such resources. Now, you might say they said that. What do we know about their actual commitment? I don't know. I just say this because I heard much talk and discussion and questioning earlier about the economics of this proposal and the financial capability of Elan and Acorda Therapeutics

to bring this off.

I can only tell what the head of the company said last night.

Finally, should this be approved by FDA, I firmly believe, as does the association, that this would be a major step in the journey towards discovering therapies, which will ameliorate and perhaps one day cure the effects of chronic spinal cord injury and multiple sclerosis.

Thank you for your time. I have brought along the person who runs our resource center, who answers most of the queries that come into the National Spinal Cord Injury Association, Bernadette Morrow, because she is the person who handles the inquiries, some not only membership, but others across the United States, Canada, Europe, even India, who call in asking about 4-AP.

Our last issue of Spinal Cord Injury Life, our quarterly magazine, the title of it was "The Status of Research, A Reason to Hope." There was mention in there about fampridine, 4-AP, and since then we have had a flurry of calls, certainly much more than we normally would have had prior to that issue about the availability of 4-AP.

I believe, just in the last week, the last three days, Ms. Morrow has had 26 calls about 4-AP. If you have any questions about how patients get answers, to what lengths they will go to get this drug, you can ask Ms. Morrow.

Again, thank you very much for your time.

DR. JUHL: Thank you, Mr. Countee and Ms. Morrow, for being here. Appreciate both your willingness to come before the committee and your patients and even with our lack of an agenda, being on time.

Our next speaker is Gina Ford, who is the executive director of the International Academy of Compounding Pharmacists.

MS. FORD: Good afternoon. It is a pleasure to see you all again. I am Gina Ford, compounding pharmacist, executive director of the International Academy of Compounding Pharmacists.

We are a 1,300 member, not-for-profit association that represents compounding pharmacists in this country. We are solely supported by the membership dues of those members.

Just to touch on something briefly that we talked about last time and that the academy has taken on as a result of requests from this committee is an adverse drug event program to be able to establish a reporting system of adverse events that might come about through compounded medications and, hopefully, we will have that process in order by the end of this year.

Five years ago, we began a fight for legislation in this country to be able to protect our rights as pharmacists, to meet individual patient needs and to do that in a manner

in which we have always talked about, which is called the triad relationship. That is now spelled out in federal law, that we must practice compounding pharmacy within that relationship, patient, pharmacist, physician.

It is very regrettable to me and I feel almost responsible for Dr. Bever's patient, who was left without that relationship of a pharmacist and a physician and that patient to be able to work together to meet the needs of that patient because that is what our goals and our missions are.

That is why I publish that 1-800 number anywhere I can so if a patient has an individual need, they can find a compounding pharmacist in their local area to work with their physicians so that we can solve those problems that they might come across.

Just briefly, I want to touch on the substances. I know that we are running late and I will be quick.

Some of the statements that were made in regards to the efficacy of 4-aminopyridine were clinically meaningful, modest efficacy or intimation of efficacy. Well, tell that to a patient that it is working for or who can now walk ten steps, who can now dial a phone and ask them if that is a modest, effective dosage that they are on or medication that they are on.

I am concerned a little bit about us looking at the economics of this and not at the patients of this. We

are pharmacists and we want to treat our patients. I can think of three products right now that were previously only available from compounding pharmacies, that were then taken through the loop and applied to the FDA and became FDA approved products. We are innovators. We started that.

There is an FDA approved product on the market now and that company is still making money. If a superior product is on the market, we as pharmacists are going to treat our patients with a superior product. So, I just want to make that very, very clear to you. We estimate that in this country there are 11,000 patients on 4-aminopyridine at this time.

I just want to make it very clear that these patients cannot go without this medication. There is no reason why this medication cannot be included on this list to be continued to have access to this medication and then when a product is brought to the market, if it is approved by the FDA, have access to that as well. I just don't want these patients to suffer in the meantime.

I just don't want these patients to suffer in the meantime. Let's put this drug on the bulk drug substance list and then work with USP to develop standards in which this drug must be compounded. That is certainly an unavailable thing to us right now.

As far as 3,4-diaminopyridine, I appreciate the numbers that were presented to you but there are approximately

a thousand more patients in this country that are receiving that drug currently. Dr. Jacobus, thank you very much. That is a wonderful program that you have, but, once again, what if there is a patient in a community and that physician and that pharmacist want to work within that community to meet that patient's need, is there any reason that that patient should have to call across the country to get that medication?

We as a community compounding pharmacist should be able to address that need locally for that particular patient.

I am afraid of some of the issues that the manufacturers are concerned about as far as stability issues and shelf life issues. That is an area where a compounding pharmacy can fill in. We don't make more medication than what it is going to be stable for.

Can they bring a product to the market that will have the shelf life to make it to the distribution center, to make it to the pharmacy, to sit on the shelf to be then dispensed to the patient? Compounding pharmacies can make products, can store products, can counsel patients with a limited supply so that we are not concerned about the stability issues at that particular time.

We are not afraid of the competition. We welcome a superior product if that is the eventual way that we are going. A manufacturer shouldn't be afraid of our competition. We are here to meet individual patient needs and those patients

whose needs cannot be met by those of the manufacturer. That is our purpose and that is what we want to be able to do.

DR. JUHL: Thank you, Gina.

PARTICIPANT: Can I make a comment or raise a question?

DR. JUHL: I would just as soon we proceed with our guest speakers of the open public portion of the hearing.

Our next speaker is Dr. Craig Basch from the Office of Paralyzed Veterans of America. Dr. Basch.

DR. BASCH: I am Craig Basch. I am with the Paralyzed Veterans of America. I am a neuroradiologist by training. We represent about 70,000 paralyzed veterans that have spinal cord or multiple sclerosis. My role is to be their medical advocate and kind of their advisor.

As far as fiscal relationships, I know that our spinal cord research foundation gave some seed money to Acorda several years ago to start that up. Other than that, I am not aware of other fiscal relationships.

As a physician, I am concerned about the data that was presented here, particularly in light of the variability and the dosages. Those numbers of 50 percent swings in uniformity worried me, particularly the 56 percent increase in dose as it may relate to seizures.

Now, as an imager, I have dealt with seizures in my training in patients who were first treated with the

anti-seizure drugs when they came out in a genetic form and seizures are bad news. People fall. They get intracranial hemorrhages. They crash cars. They hurt themselves with heavy equipment and our members are very active and that is a big concern of mine.

Having said that, I also realize that we have a lot of our patients who take this drug, want this drug and realize benefit from it. When I had my own spinal cord injury, I realized that very subtle changes in neurologic function make a big difference in the patient's lifestyle, which are not measurable on the clinical level. So, that is important.

Weighing those risks and benefits, the official PVA position is that we support the open label method of distribution for our patients as a way that would be reasonably safe and increase your access to the pharmaceutical.

DR. JUHL: Thank you.

Our last speaker in the open session is Jackie Havner.

MS. HAVNER: My name is Jackie Havner and I am 58 years old and I have had MS for 34 years. I have to say that I have been on -- lucky, I was put on a study five years ago of fampridine and I own three wheelchairs and I own multi canes. I still could walk, but I couldn't walk very well and I couldn't walk very far and I couldn't walk without assistance and there were a lot of things I couldn't do.

Now I can lean down and get things off the floor.

I can even dance. So, it is really fabulous. While I think everybody should be able to get the medication, I happen to be fortunate I am on the compassionate use -- in fact, I was really sort of squirming almost, but I just feel that it really needs to be controlled. I was very nervous that I wasn't going to be able to get it and I thought I would definitely go on the pharmacy compounded stuff, but I was terrified. I was really terrified.

I think I would make the analogy of saying I had a husband with cancer and, you know, the difference between MS-IR, which is immediate release and MS-Current, which is continuous release, you know, I could have killed him with the immediate release. On the other hand, he had to have the immediate release to begin with. So, I would say the same thing, kind of -- at least that is how I feel about the pharmacy compounded 4-AP because seizures are pretty horrible things and some of the side effects that I know about that friends of mine have had friends who have experience in this kind of thing, who have been on this because, of course, if you couldn't get it on the study, you wanted to go get it at the pharmacy.

But I really feel that this does not belong on the compounded list, for whatever it is worth, but I really want to see it available because I don't want to get off of it.

Thanks.

If you have any questions I will be glad to answer them.

DR. JUHL: Thank you very much.

Okay. Are there any other members of the public, who would like to address us, who didn't register with us in the beginning?

I think we will wait until the discussion period. I want to reserve this period of time for the general public.

Seeing none, let me ask the pleasure of the committee. I think our discussion would go probably more rapidly if I didn't ask if you needed a bathroom break, but I will do that anyway. Do you want to take two minutes or are you ready to proceed with the discussion?

MR. BASCH: Just one last comment.

My comments about the open label, which is to support the Acorda-Elan expanded process. That was clear, I think, wasn't it? Yes, I thought so.

DR. JUHL: Break or no break? Help me out here.

Okay. We have two people that want a break and more that don't. So, we won't.

Let's go to the discussion portion.

Agenda Item: Discussion and Vote on Neuropharmacological Drug Products

Shall we do last in, first out? In my mind, the 3,4-diaminopyridine is more recent in my mind. Let's do that

one first and then move to the aminopyridine. Okay?

Let me try and summarize and, again, start leading us as far as we can go and see what I think you think.

One, we have a serious illness. Secondly we have a drug that shows some promise and certainly has some effect for some patients. We have a need for more information. We have in all likelihood some questions of drug stability and so on. This is a difficult to compound product and it requires refrigeration. We have a company who has an in-place distribution program that they are volunteering to make a wider access program from.

Are all those parts of the things that we understand we understand? Then it would seem we are at the question that is similar to what we had this morning is to recommend that the drug be listed on the bulks list available for pharmacy compounding or that the drug not be listed on the bulks list with the recommendation that the FDA pursue the expanded access program with the manufacturer and doing as they would normally do, make sure that those patients who are on the drug now are not disadvantaged.

DR. LIEBMAN: Question, please.

DR. JUHL: This, too, we would like to hear back on how the progress is in the development of a program by our fall meeting.

Yes, David.

DR. LIEBMAN: Did I understand that there are another thousand patients out there?

DR. JUHL: Yes.

DR. LIEBMAN: Can the manufacturer, can Jacobus pick up a thousand patients, a thousand additional patients. If we make it unavailable through compounding, will Jacobus have the ability to pick up a thousand extra patients?

DR. JACOBUS: We probably have two-thirds of that population now of sulfapyridine that Dr. McBurney spoke about. It is easier to ship.

I would like to ask Dr. Sanders whether there really are that many out there. We have no indication of that. We certainly technically could do it. Right now, we are paying the full cost on it and probably -- I don't contemplate that expense with any degree with pleasure.

DR. LIEBMAN: I guess my thought is there were a thousand patients --

DR. JACOBUS: Technically, the answer is easy. Yes. Money-wise, it is always hard because we survive only on what we sell.

DR. LIEBMAN: How do we move those thousand patients who are currently getting medications through compounding and their physicians into your system with a fair amount of smoothness.

DR. JACOBUS: The patient would have to see the

physician. Presumably, the compounding doesn't take place absent a physician's script.

DR. LIEBMAN: Correct. I would imagine -- of course not. You can't compound without a physician's prescription.

DR. JACOBUS: I hope so.

DR. LIEBMAN: Yes.

DR. JACOBUS: I don't know whether those -- we don't have any intimation that there is that kind of a requirement out there.

The physician then has to call and say I have this patient. Here are the data. The patient should be registered and we will register the patient and ship the medication the next day.

The physician will not be allowed a refill unless we receive the data that everything is squared away. That is our proposal. If there is a great backlog of patients that we wonder about, whether the diagnosis is true, then I think we might require all the information in first, but we do expect to receive from the physician a letter comparable to what a physician will write a family practitioner on returning a patient or the physician will write to the Agency transmitting the information we expect to receive before we will ship clearcut report that the patient has the diagnosis.

If the patient is already on it, we would expect to receive evidence that the patient needs to stay on it.

In other words, there might be patients that got on it just because of awareness and desperateness and no follow-up. 3,4-diaminopyridine can be stopped and very few patients will be -- I mean, they will be weaker, but very few patients are dependent on breathing machines and they will be -- I don't think there are that many patients. If there are, we will do it.

DR. JUHL: Does that answer your question?

DR. LIEBMAN: My only thought is that a reasonable expectation. Are you going to have 500 doctors or 700 doctors across the country now writing letters requesting that the patient --

DR. JACOBUS: Well, we had that in sulfapyridine. We had 10 percent of the American Academy of Dermatologists participating in that program. And the answer was it was a real squeeze at the start.

DR. LIEBMAN: I only raise the issue. It is not a question of you can or you can't. I just raise the question. That is all.

DR. JUHL: Sarah.

DR. SELLERS: I just wanted to clarify that we are still under the assumption that another IND could be obtained from a physician for this use or for another use or another indication or are we saying that the only way to obtain this drug now would be through --

DR. JUHL: No. Another IND is always possible.

DR. SELLERS: Okay.

DR. JUHL: Loyd.

DR. ALLEN: Just for clarification, as we look at this then, we have a system which has been in operation for x number of years, where the material is available through Jacobus, number one. Secondly, it is available through compounding pharmacies. This is all ongoing until the point in time that we will have a commercially available product on the market.

I guess my concern would be changing what has been reasonably effective for these patients that are out there, possibly putting them and their physicians into an area requiring extra effort when with the 3,4-DAP, we have not seen any significant safety or efficacy concerns from the patient's standpoint. I am not sure that it would be necessary to change what is ongoing until the point in time that the product is commercially available.

DR. JUHL: I think the argument is and it is a valid argument that by moving many more patients onto the protocol, your safety data would be collected more rapidly and it would speed the product's approval rather than delay it.

If you look five years out and, say, okay, the drug is approved today, we will know more about it. I think there is that advantage that counterbalances that. I think

your point, though, too, is good. Is there enough time between now and then to -- the bureaucracy changeover will cause some struggle for a period of time. My suspicion is it will take long enough for this drug to get approved that there will be a real advantage to having a greater number of people in the safety database because right now, unfortunately, the compounded products, there is no data collected on those patients and I was impressed with the requirement and your stick-to-itiveness on getting the data back in order to provide drug.

Dr. Gilman.

DR. GILMAN: We have heard from good authority that the drug is effective. We have also heard a good deal about its safety with respect to at least those patients who have been treated with doses lower than 80 milligrams per day. So, I think the real question is whether additional data are needed with respect to safety.

Would it be better to have an IND and not allow the drug to be compounded, so that there would be a central distribution site, central provider for the drug and an enforced requirement essentially that all concerns with the drug, all seizures be reported? I think that is really what it amounts to because it certainly sounds safe.

MR. TRISSEL: It sounded to me like the burden, whatever there is, is going to fall largely on Dr. Jacobus

and his group because they will be all coming in. It doesn't sound like the burden on a physician with one or two patients is particularly severe to get on the program.

DR. JUHL: Dr. Katz and then Dr. Rodriguez.

DR. KATZ: Again, with regard to safety, I guess we heard that where -- that the patients who were receiving it through compounding, we haven't heard any problems about them, but that is part of the problem. We haven't heard. There is no obligation on anybody's part who would be treating those patients with compounding, that they report any problems.

They are not in the system. So, again, just to reiterate, one of the great advantages of having this all subsumed under an IND is that there are reporting requirements and we will -- and physicians will be required to follow the patients closely and report bad things that happen.

So, right now I would say of the patients who were under the INDs, we know there really aren't any problems below 80 milligrams or whatever dose. But in patients outside the IND, however many there are, we really have no idea what the experience has been.

DR. RODRIGUEZ: First, let me say up front I like the idea of the data collection in an organized fashion. This is going to make a 7 1/2 fold increase in the shipment of this drug compared to what you have got at this moment, but you possibly have proven that already in another system.

This drug is going to be prescribed only by neurologists, I would assume, because the one concern that I have is those -- maybe it is small, 5 percent, 10 percent, who are now receiving their medication, whose forms are not being filled up and, therefore, no form, no drug.

Now they are getting the drug and the question is what recourse do those patients have then? Storm the neurologist's office?

DR. ALLEN: Just one real quick question I had when Dr. Jacobus was doing his presentation on dosage modification or dosing adjustment, how many strengths is the DAP available in?

DR. JACOBUS: Right now it is in 10 milligram strength with a -- it is a scored tablet. So, that gives you options.

DR. ALLEN: Okay. Thank you.

DR. JUHL: I wasn't sure that I understood Dr. Rodriguez's comment or if I was expected to respond to it, but I must confess that I didn't quite -- if he wants to ask it again, I am totally interested.

DR. RODRIGUEZ: No. I just had a question, first of all, about the increase, which was 7 1/2 fold, but I figured that -- Ray has shown that you could do it at least with the previous study. My study was what percentage of patients might be put at risk.

DR. JUHL: I remember.

Remember one other thing, too, I think --

DR. RODRIGUEZ: In your past experience with the previous drug, what was the percentage of people that were not turning in or you had to call and say if you don't send me the medication, you don't get the drug? In other words, what were the outliers that did not send the information?

DR. SANDERS: It occurs.

DR. JACOBUS: There was an element of your question, though, that was relevant. There are, for example, doctors of osteopathy, who may not be members of the American Academy of Neurology, who have a strong interest in the subject and are totally competent. There are some -- there is an analogous groups to the American Academy of Dermatology and we allow those -- and there are some general practitioners, who we think are absolutely clear on, at least in dermatitis herpetiformis it is a relatively rare disease, but they are skilled that way.

So, we make it -- we have in the past -- perhaps I shouldn't say that in the presence of all these Agency people, but we have said and we have written it into the other protocol that the invitation is to the members of the professional academy, but if there is somebody who has produced the data and is managing the patient, we think that is fair enough.

We accept the patient. We often -- they will send

us a C.V. and a license and we will send them the mint.

DR. JUHL: Other questions or comments or opinions?

If it is absolutely necessary -- I would like to limit discussion to the committee.

DR. SANDERS: It is not absolutely necessary, but I would just like to comment on the referral patterns that I would predict would happen with DAP if it were made available under this program. And I think I have some expertise in that.

This is a rare disease. Not many physicians ever see it and very few are very comfortable dealing with it. I would predict that most neurologists in practice would prefer to refer a patient with this condition to someone who has seen a few patients with it. So, I think probably what would happen, if it were not available to any physician who could write a script is that they would find who in their local community or nearby had dealt with these patients, refer them to them and let them deal with the issue of getting the drug.

DR. JUHL: Are we ready for the question? Are we clear on the options? Option 1 is to recommend the drug be listed. Option 2 is we recommend the drug not be listed. All those favoring Option 1, please raise your hand. I see four hands raised.

Those preferring Option 2, please raise your hand.

Seven for Option 2. So our recommendation with a split vote is that the drug not be listed and the FDA pursue the opportunity to have an expanded access program that would serve at least as many patients that are on the drug now.

Shall we move to 4-aminopyridine. We have the same kinds of issues with this drug. We have, I think, with this drug more evidence of difficulty in the compounding of the product, but we have less information on the company's ability to put the program into operation and it would be from my guess a bigger program to put in operation because of the numbers of patients.

We had some discussion about whether or not there is a thousand patients to be dealt with Lambert-Eaton. Are there, indeed, 10,000 patients that would need to be dealt with for 4-aminopyridine?

Do you have an estimate of --

DR. COHEN: None of the figures are definite now, just because of the nature of the fact that people are getting at the compounding. So, there aren't really records, but from a number of different sources, Elan actually commissioned a market analysis group to look at this a few years ago. I think there are other -- we have had input from various physicians who have in turn worked with some of the compounding pharmacies. Our best guess now, just based on all of these different inputs, which seem to agree with one another, is

that that there probably are 10,000 or so and perhaps more than 10,000 people, who are using compounded formulations now. Those numbers are in all likelihood increasing now as the publicity surrounding the work, the clinical development and so on and some of the spinal cord injury and multiple sclerosis advocacy groups are getting word out, just tracking what is going on.

So, our sense is that it is likely to be around 10,000. It is possibly more than 10,000 and the numbers are probably growing. I should also tell you that we have -- in response to some earlier questions, we have looked at the logistics for supplying this for up to 20,000 so far, based on our sense of where things are. We are quite comfortable that together with Elan we can supply that in an expanded access study. Again, that doesn't mean that that is what the number would be and I will also reiterate that we need to work closely with the FDA to discuss with them what the regulatory parameters are around such a study.

But in terms of our capability and our desire to supply this, we have already done the math, as it were, on up to 20,000.

DR. JUHL: Could you contrast and compare how you envision your distribution program with that of Dr. Jacobus?

DR. COHEN: My sense is that we are talking about two very different animals. Again, I am by no means an expert

on Lambert-Eaton Syndrome or the demographics of that syndrome, but based on that data that have been discussed here today, in the case of Lambert-Eaton, we are talking about a population that numbers apparently in the hundreds. It is a truly very rare condition.

The issues in distribution, therefore, may or may not be comparable because in the case we are discussing with multiple sclerosis and spinal cord injury, clearly, we are talking about, as I said, 10,000 or on that order of magnitude and, again, from our perspective, we certainly are not equipped as a company nor is Elan and nor would I say are many, even major pharmaceutical companies equipped on their own to run these kinds of studies. These are special circumstances and even in the cases of some of the major pharmaceutical companies who ran studies for HIV drugs, expanded access studies for HIV drugs and so on, they worked with some of the contract research organizations that we are also talking with now.

So, from our perspective, this is very much manageable, using an expert group that is outfitted to do this and has experience in doing it and really our obligation in that case is to work closely with them to exchange the appropriate information, to supply the drug in the appropriate form, which we can do with Elan as our partner and then to collect the data from them and assimilate it and pass it on to the agency under our IND.

MR. CATIZONE: I would speak in favor of not listing this product on the list of substances approved based solely on the safety data presented by the FDA prior to this meeting. I am uncomfortable accepting the data that was presented at this meeting regarding the compounded products by pharmacists because I feel that that data may be biased and unfair.

I am also disturbed by entities, which hold patients hostage and this committee hostage in situations where patients can be at risk and would commit that NADP would urge its members and work with its members to take whatever legal actions it could to ensure that patients' medications and therapies would not be interrupted in situations like this.

DR. GILMAN: I think there is a big contrast between 3,4-DAP and 4-AP, with respect to both efficacy and safety. The studies with respect to efficacy are highly questionable with respect to how good this medication really is, how much function do patients, most patients, really get. They may show some improvement on a scale. That doesn't mean that any but the unusual patient is really that much better with the medication.

And we are hearing about very variable levels of blood levels and dosage levels that provoke seizures. Here, I think, we really need systematic, carefully collected data with good reporting with respect to adverse events, as well

as efficacy.

So, this one is much more clearcut from my perspective than DAP. I think this certainly ought not to be on the list.

DR. JUHL: Other comments?

Are we ready for the question?

DR. COHEN: Could I make one more comment in response to something that was said?

You know, the term "holding patients hostage" was used earlier and I certainly don't want to get into an escalation of that particular debate. I do want on the record to say that at the end of the day, we at Acorda and Elan are interested in the welfare of our patients. We have very strong relationships with the community patient groups, who work in this area. You have heard from some of them today. There are others out there. We try to be as responsible and good citizens in this regard as we possibly can in terms of supplying them with information about what we are doing and doing the right thing.

I just wanted to illustrate for the committee or for the panel one illustration of why this is for us not so clearcut in terms of how and when, under what circumstances one supplies patients with an experimental compound. I will tell you and I will go out somewhat on a limb because we have not yet submitted this to the FDA, but I do want to try and share this with the panel, that in our studies, even in chronic

spinal cord injury, we were very surprised to find -- these were placebo controlled, double blind study -- we were very surprised to find the extent to which patients apparently experienced remarkable benefits under placebo, never having had the drug at all.

I am talking about people who were injured for five years, who suddenly one week opened their hand for the first time and grabbed a glass of water. I am sure that all of you have the same response to this that we did, which is as soon as we saw it before we broke the blind, we said my goodness, that is fabulous. We have just a remarkable drug effect here.

There was no question that it was placebo. There was no mistake. The blood levels, the plasma levels showed it. It was the same sequence. So, I think when we are talking about how we address our patient population here and taking into account their welfare, I just want to put a plea out that we all remember that these things in clinical medicine are hardly ever cut and dried and one sees remarkable things that one would never imagine you would see under other than the influence of the drug itself, but you do see it.

So, we want to be as careful as possible. Frankly, the idea of investing tens of millions of dollars to try and get a drug approved that we may or may not be able to get approved is not -- it is not the most appealing occupation in the world, but we are doing it because we do believe in

the drug. We believe we will be able to show these things, but we also believe we need time. We need to do the right studies. We need to cooperate with the Agency and we need to do it in the right way and that putting this drug out ad lib for anybody in an uncontrolled fashion is not going to be doing anyone any favors and least of all our patients.

So, I just wanted to put that on the record. Thanks.

DR. ALLEN: 4-AP is similar to the 3,4-DAP. It is not the anybody is putting something out there. It has been out there for years, in fact, 10 or 11,000 patients are on it right now. Again, what this does is it alters their method of obtaining the drug, whether or not they can obtain it. That would be one of the things, you know, that I would be concerned about.

DR. JUHL: Seeing no more questions, let's call the question with the same two options. Option No. 1, recommendation to list the drug on the bulk compounding list. Option No. 2, recommend the drug not be listed and ask that the FDA would pursue an expanded access program for the drug that would not inconvenience patients who are already receiving it.

MR. TRISSEL: Dr. Juhl, just one point for clarification.

If we vote for the latter option and the program does not materialize, what recourse do we have at that point

because now we voted to put it on this list and the program that we were banking on didn't happen. Is there an alternative to that?

DR. JUHL: I believe that the FDA would pursue something and not just let the patients all go wanting.

DR. BEHRMAN: Again, as I tried to say before, we believe there are two questions here. One, is it appropriate for the list and that question has to be answered. Then if the answer is "no," you have our assurance that we will make every effort that patients who need access -- that doesn't necessarily mean everyone who wants it, but depending on the appropriateness, the safety of the drug, et cetera, we will make every effort to make sure that such a program is in place. Again, the Agency cannot require programs.

I can think of very few companies that have initiated large programs this early in development, but it has been done and has been done successfully.

DR. JUHL: Ready? Okay. Those who favor Option No. 1, please raise your hands. We see two votes. Those favoring Option No. 2, raise your hands. Nine favoring Option No. 2. Okay.

We are six minutes over budget. Again, for those members of the staff who weren't here earlier, I want to thank you for the efforts that you put in preparing us for today's meeting and certainly my thanks to the committee for bearing

with us, as well as those guests who made presentations to us.

The committee will adjourn and meet again tomorrow morning at 8:30.

[Whereupon at 5:06 p.m., the meeting was recessed, to reconvene at 8:30 a.m., the following morning, Friday, May 7, 1999.]